Green Pharmacy in Pharmaceutical Processes

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Abstract

The application of green pharmaceutical practices during pharmaceutical processes strive to minimise the environmental impact of the pharmaceutical industry. The study aims to evaluate the application of green pharmaceutical practices within the local pharmaceutical manufacturing industry and to develop a tool to assess the greenness of an API manufacturing process.

A set of questions were developed and validated by a panel of experts and applied during structured interviews with stakeholders to discuss the use of green pharmaceutical practices, challenges and barriers in implementation. Data collected was analysed thematically. Criteria to be included within the tool were identified through a literature review. The developed tool to quantify the greenness of a process was validated via a focus group consisting of four members having experience within the active pharmaceutical ingredient manufacturing industry. A pilot study was conducting utilising green and conventional pathways found in literature as well as using a shelved synthesis pathway in collaboration with a manufacturing site.

Seven out of the 16 companies which satisfied the inclusion criteria agreed to participate in the study. The API manufacturing site was noted to implement wastewater treatment systems (WWTS), green solvents, solvent recovery, one pot synthesis and environmental assessment methods. Finished dosage form manufacturing sites implemented environmental assessment methods (n=2), renewable energy (n=2), paperless approach (n=3) and WWTS (n=1). Barriers and challenges in implementing green practices included financing (n=4) and regulatory aspects (n=3). Criteria identified for inclusion within the greenness assessment tool included raw materials, catalyst, solvent type and amount, percentage yield, atom economy, cleaning steps and solvent classifications and

the waste generated. These criteria all have an individual score which in total give an indication of the greenness of a process.

The study shows that company size has an influence on the ability to apply, fund and incentivise green practices with large and medium sized enterprises being more willing. A factor noted that impacts application of more sustainable methods was whether processes were developed locally on site. Validation of the scorecard by comparing a green and conventional synthesis pathway confirmed the ability to evaluate the greenness of a process.

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List of Abbreviations

ACS GCI	American Chemical Society's Green Chemical Institute
API	Active pharmaceutical ingredients
CO_2	Carbon dioxide
ERA	Environmental risk assessment
FDF	Finished dosage forms
GHS	Global Harmonised System of Classification and Labelling of Chemicals
GMP	Good manufacturing practices
GSK	GlaxoSmithKline
HMIS	Hazardous Materials Information System
HVAC	Heating, ventilation and air conditioning
LCA	Life cycle assessment
MC	Medical cannabis
WWTS	Wastewater treatment system

Chapter 1

Introduction

The health sector is responsible for 4.4% of the global net emission, equivalent to 2 gigatons of carbon dioxide (CO_2).[1] Of these emissions, the biggest contributors include China, the United States and the collective countries making up the European Union (EU).[1] Looking at the local scenario, the health care sector is responsible for 4.8% of the national net emissions, considered an above average emitter per capita.[1] As of 2015, it was estimated that the aggregate global emission produced by the pharmaceutical industry amounted to 52 million metric tons of CO_2 (Belkhir & Elmeligi, 2019).

1.1 Pharmaceutical pollutants

The presence of pharmaceuticals in the environment have been detected in the environment since the 1970s (Kümmerer, 2010). The pharmaceutical industry is a key factor responsible for pharmaceutical pollution (Daughton & Ruhoy, 2010; Sammut Bartolo et al, 2021).

Environmental pharmaceutical pollution relates to the detection of active pharmaceutical ingredients (API's) and their metabolites in soil, water, such as surface and ground water, and the atmosphere (Parezanović et al, 2019). The effect of the pharmaceutical products depends on the nature of the product, toxicity, length of exposure, half-life and the concentrations at which they are present in the environment (Parezanović et al, 2019).[2]

Each stage of the life cycle of the medicinal product relates to this issue of pharmaceutical pollution (Fig.1). Activities within the pharmaceutical industry contributing to the

[1] Health Care Without Harm. Health Care's Climate Footprint [Internet]. 2019 [cited 2024 Jul 27]. Available from: https://noharm-europe.org/content/global/health-care-climate-footprint-report

[2] Mudgal S, De Toni A, Lockwood S, Salès K, Backhaus T, Halling Sorensen B. Study on the environmental risks of medicinal products [Internet]. 2013 [cited 2024 Jul 27]. Available from: https://ec.europa.eu/health/sites/health/files/files/environment/study_environment.pdf

environmental contamination include research and development, chemical synthesis, fermentation processes, natural product extraction and formulation processes required in drug manufacturing (Brems et al, 2012). Following manufacturing, API's and metabolites are dispersed into the environment due to excretion by humans and animals as well as the inappropriate disposal of medications (Boxall et al, 2012; Toma & Crisan, 2018; Vatovec et al, 2021).[2] The overuse of medicinal products in livestock results in pharmaceutical products being detected in soil due to excretion which can contaminate water sources and be ingested when consuming such livestock (Boxall et al, 2012; Parezanović et al, 2019).

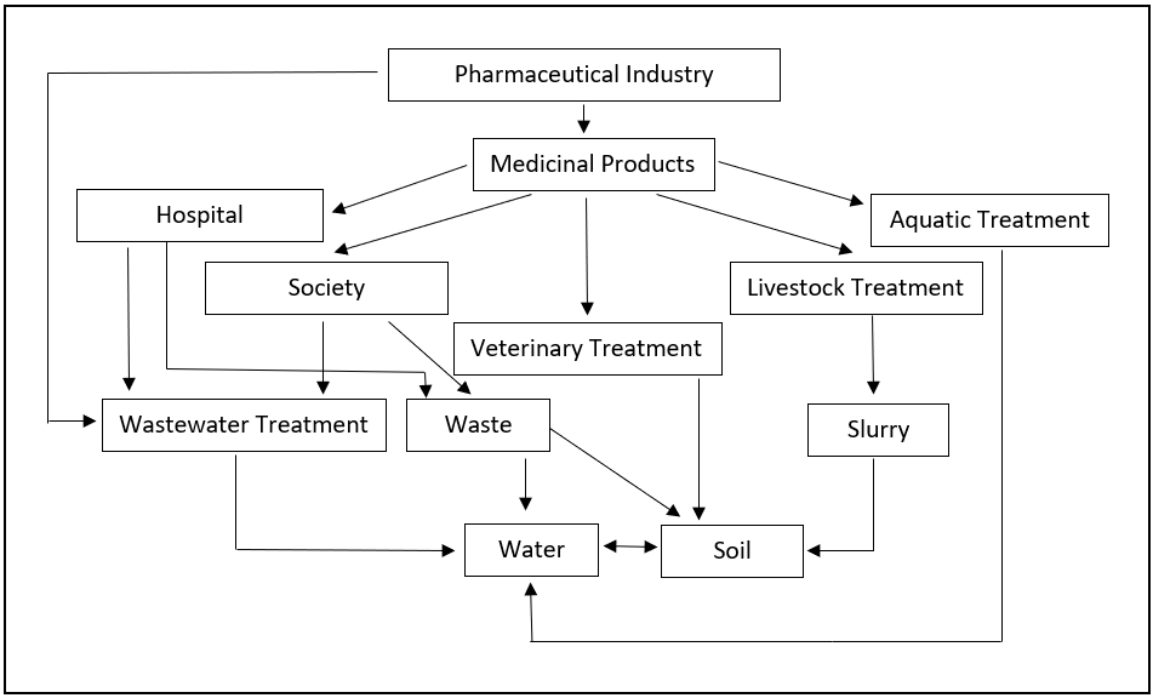

Figure 1: Entry of medicinal products into the environment

(Adopted from: Kümmerer K, Hempel M. Green and Sustainable Pharmacy, 1st ed. Springer-Verlag Berlin Heidelberg;2010. p.212 and Boxall A, Rudd M, Brooks B, Caldwell D, Choi K, Hickmann S, et al. Pharmaceuticals and Personal Care Products in the Environment: What Are the Big Questions? Environmental Health Perspectives. 2012;120(9):1221-1229)

The consumption of pharmaceutical products has increased globally and is said to continue along this trend as the need to treat age-related and chronic conditions rises (Gonzalez et al, 2021). This increased global consumption is proportional to the

increasing number of pharmaceutical pollutants and metabolites being detected within the environment (Aus der Beek et al, 2015). Despite the positive effects of pharmaceutics and their use as therapeutic agents in the treatment of patients, when leaked into the environment, these become an issue of concern due to the damaging and hazardous effects on humans, animals and the environment (Cunningham et al, 2009). Pharmaceutical pollution also challenges the health sector due to resistances which may form due to subtherapeutic exposure. This is true to antibiotics were their subtherapeutic presence in the environment has led to bacterial resistances, resulting in less therapeutic choices for certain infections (Bondarczuk et al, 2015; Kamba et al, 2017).

Drug classes which have been detected at subtherapeutic levels in aquatic environment include antiepileptics, anti-inflammatory drugs, antibiotics, antidepressants and betablockers amongst other commonly used API's and metabolites (Heberer et al, 2002; Nikolaou et al, 2007; Zhang & Geißen, 2010; Barra Caracciolo et al, 2011; Gamarra Jr. et al, 2015).Trace levels of API's such as oestrogen ethinyl estradiol has led to changes in marine populations through the feminisation of fish (Sangion & Gramatica, 2016).

1.2 Green pharmacy

This growing knowledge with regards to the impact of pharmaceutics on the environment and the increased awareness of the environmental changes has resulted in new methods and approaches to create a more sustainable and green pharmacy (Clark et al, 2010). Green pharmacy focuses on designing pharmaceutical products and processes that facilitate the reduction or elimination the use and generation of hazardous substances along the product's entire life cycle (Toma & Crisan, 2018). Novel design in the pharmaceutical sector is a necessity to decrease the environmental impact of

pharmaceuticals. Rastogi et al (2014) uses the beta-blocker metoprolol to illustrate how changes to an existing chemical molecule can be made to form a greener pharmaceutical product which is more biodegradable. It is emphasised that although these design approaches still require further research, it is a way towards a more sustainable pharmacy (Rastogi et al, 2014).

1.3 The 12 principles of green chemistry

Anastas and Warner (1998) were the first to coin the term green chemistry and developed what are commonly known as the 12 principles of green chemistry (Table 1). Green chemistry is described as a means of preventing pollution through the decreased use or elimination of hazardous chemicals in the industrial life cycle of a pharmaceutical product (Anastas & Warner, 1998).

Table 1: The 12 Principles of Green Chemistry

(Adapted from: Anastas P, Warner J. Green Chemistry: Theory and Practice. Oxford: Oxford University Press; 1998.)

1. Reduction and prevention of waste	7. Use renewable feedstocks
2. Maximise the use of all atoms in the rection in the final product (atom economy)	8. Avoid derivatisation
3. Use of less hazardous and toxic substances	9. Use catalysis instead of stoichiometric reagents
4. Design and use of safer chemicals	10. Design drugs which do not degrade to form toxic products in the environment after use
5. Reduce use of auxiliary substances and use safer ones when needed	11. Real-time pollution prevention
6. Use the most energy efficient route	12. Substances used should be safe and minimise the possibility of accidents

The development of the 12 principles of green chemistry forms the guidelines used by chemists in the formation and optimisation of green pharmaceutical products (Anastas & Kirchhoff, 2002). The focus of these principles is the prevention of environmental pollution through the decreased use or elimination of hazardous chemicals while still maintaining a manufacturing process which is efficient, cost effective and practical (Anastas & Warner, 1998).

Similarly, green chemical engineering incorporates the concept of 'benign by design' in relation to the design and process of new products, giving importance to energy consumption (Anastas, 2003; Garcia-Serna et al, 2007). The 12 principles of green engineering form a framework of what is considered the most sustainable, energy and cost-efficient design process of a product throughout the whole life cycle starting from the acquisition of materials to the manufacturing process (Anastas & Zimmerman, 2003).

1.4 Aim and objectives

This study aims to evaluate the green practices adopted within the local pharmaceutical manufacturing industry. The objective of the study is to seek stakeholders' knowledge and opinion on green practices, including solvent use and wastewater treatment processes, as well as challenges and barriers in their implementation. The study will aid in identifying any opportunities for improvement of currently applied practices within the pharmaceutical industry by proposing alternative solutions to shift to a more sustainable approach. The study aims to develop a tool to assess the greenness of API manufacturing processes.

Chapter 2

Methodology

The study methodology consisted of two phases. The first phase involves the development of a set of questions and structured interviews conducted with stakeholders within the pharmaceutical manufacturing industry. The second phase of the study included collaborating with an API manufacturing facility to develop a scorecard to assess the greenness of a manufacturing process.

2.1 Phase 1: Structured interviews

A literature review was conducted to identify green practices implemented within the pharmaceutical industry. This was carried out by searching for related terms such as "green pharmaceutical practices", "green chemistry" and "green pharmacy" using the databases Google Scholar, PubMed and Hydi which is a collection of databases available at the University of Malta. Articles were analysed according to relevance to the topic in question. A set of questions for the structured interviews were developed to evaluate the applications of green practices utilised within the local pharmaceutical manufacturing industry, including solvent use and wastewater treatment systems (WWTS) as well as challenges and barriers in their implementation.

The developed set of questions (Appendix 1) were validated by a panel of three experts consisting of an academic pharmacist, an expert in API manufacturing and a qualified person in solid dosage forms. Each question was evaluated for the degree of relevance and clarity. A scale between 1 and 4 was used to establish the degree of relevance and clarity, where 1 indicates that the question is not at all relevant or clear and 4 indicates that the question is highly relevant or very clear. The validation panel was requested to give any further comments and recommendations which they felt necessary for each individual question. The validation panel was questioned if the research question is

answered, if all issues pertaining to the research question were included and if the sequence, structure and length of the developed questions was acceptable. Comments and recommendations were noted, and appropriate changes were made in reference to suggestions made.

A point system was used to validate the questionnaire following all responses. A question given a score of 1 or 2 was given a mark of -1 while a question given a score of 3 or 4 was given a mark of +1. An average was used to note if the response was negative, positive or neutral in relation to the degree of relevance and clarity. Changes were made accordingly.

The developed interview questions consisted of two sections. The first section related to the company demographics of which respondents were questioned about the number of employees within the local facility, annual turnover and the balance sheet value which would allow extrapolation of the company size.[3] The second section of the interview questions related to the green pharmaceutical practices identified through the literature review. The stakeholder's knowledge on green practices and which green practices are implemented within the facility was sought. The questions sought the stakeholder's opinion on current issues including the introduction of Good Manufacturing Practices (GMPs) that outline standards for discharge of pharmaceutical residues, quality marks for pollution control on imported API's and raw materials, and the Environmental Risk Assessment (ERA) as a criterion for refusal. The opinion on the introduction of incentives, their effectiveness in innovation of green practices and the willingness of a company to pay to aid research and provide educational campaigns was also sought.

[3] European Commission. Commission Recommendation of 6 May 2003 concerning the definition of micro, small and medium-sized enterprises. [Internet]. Official Journal of the European Union 2003 [cited 2024 Jul 25]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32003H0361

The study was registered with the University of Malta Faculty Research Ethics Committee [MED-2023-00491] (Appendix 2).

Participants for the structured interview were identified by referring to the list of local pharmaceutical manufacturing companies issued by the Malta Medicines Authority. Companies considered relevant for inclusion in this study were local manufacturers of API's, finished dosage forms (FDF) and medical cannabis (MC). Companies with secondary manufacturing activities were excluded from this study. Participants were first contacted by email and then by phone using the contact information available on the company websites. Structured interviews were held in person or virtually with stakeholders within the pharmaceutical industry to discuss green practices applied and the waste management of the facility. Data collected was analysed by grouping responses thematically.

2.1.1 Publications of findings

An abstract entitled "Green Pharmaceutical Practices in Industry: A review" was accepted as a poster presentation for the 82nd FIP World Congress of Pharmacy and Pharmaceutical Sciences, which was held on 1st to 4th September 2024, in Cape Town, South Africa (Appendix 3 & 4).

2.2 Phase 2: Greenness assessment tool

The second phase of the study included conducting a literature review to identify criteria to be included within the tool to define parameters to quantify the greenness of an API manufacturing process. Possible guidelines and classification systems from which scores

based on hazards and environmental impact could be utilised were identified. Amongst these the CHEM21 and GlaxoSmithKline (GSK) solvent selection guidelines, Globally Harmonised System of Classification and Labelling of Chemicals (GHS) and Hazardous Materials Information System (HMIS) classifications systems were identified (Adler et al, 2016; Prat et al, 2016).[4,5] A scorecard was developed such that for each criterion identified, a score may be calculated and that each step of the synthesis pathway is accounted for.

Methods of calculating the scores for the identified criteria were developed. These were developed based on the GHS classification regarding the raw material, catalyst and waste type scores, which can be obtained from safety data sheets and the database "PubChem".[4,6] An alternative method of calculating the raw material score was developed utilising pictograms present in safety data sheets. The GSK solvent sustainability guide was utilised to classify the solvent utilised, by which a summation equation of the waste, environmental impact, health, flammability and reactivity equate to the solvent classification score.

2.2.1 Green assessment tool validation

Validation of the greenness assessment tool was carried out by conducting a focus group discussion with four participants, three process scientists in research and development

[4] Classification and labelling (CLP/GHS) - European Commission [Internet]. single-market-economy.ec.europa.eu. [cited 2024 Jul 28]. Available from: https://single-market-economy.ec.europa.eu/sectors/chemicals/classification-and-labelling-clpghs_en#:~:text=The%20United%20Nations

[5] HMIS® — American Coatings Association [Internet]. web.archive.org. 2024 [cited 2024 Jul 29]. Available from: https://web.archive.org/web/20240408020503/https://www.paint.org/programs-publications/programs/hmis/

[6] PubChem. PubChem [Internet]. Nih.gov. National Library of Medicine; 2024 [cited 2024 Aug 20]. Available from: https://pubchem.ncbi.nlm.nih.gov/

and an advisor, all having experience within the API manufacturing field. During the focus group, the aim of the tool, key features found in literature and an explanation of the tool were presented. Participants were asked to give their opinion on the relevance and applicability of the tool developed. Opinion on what criteria may be further included or may not be relevant in practice within the manufacturing industry was sought. Changes to the tool were implemented according to feedback obtained through this focus group discussion.

2.2.2 Pilot study

The tool developed was further validated by testing a green and conventional synthesis pathway for respective products which were identified through literature. This was followed by conducting a pilot study using a synthesis pathway for a product whose production has been shelved. For the discretion of the collaborating company, this product will be referred to as product X.

Chapter 3

Results

3.1 Green practices in manufacturing

The green pharmaceutical practices utilised within the manufacturing industry identified through the literature review were mainly related to four broad categories, namely, solvents and their use, wastewater treatment systems, renewable energy and green chemistry.

3.1.1 Solvents and their application

Solvents amount to 80-90% of the mass of pharmaceutical agents used for API manufacturing (Constable *et al*, 2007; Grodowska & Parczewsk, 2010). Solvents can be classified as inorganic, therefore not having a carbon moiety within the structure, or organic solvents (Yaseen *et al*, 2021). Organic solvents, including alcohols, ethers, ketones and halogenated solvent, are amongst the most utilised solvents per amount of final product (Grodowska & Parczewsk, 2010; Savelski & Slater et al, 2017). These are often necessary for majority of the processes in the manufacturing of pharmaceuticals such as in solubilisation as a reaction media, separation, purification and the cleaning of equipment (Grodowska & Parczewski, 2010; Yaseen et al, 2021).

Organic solvents pose both environmental and occupational hazards. Long-term exposure of these solvents has harmful effects on human health due to their carcinogenicity, reproductive hazard and neurotoxic nature (Joshi & Adhikari, 2019). Organic solvents enter the environment through air emissions, industrial and waste-treatment discharge, accidental spills and inappropriate disposal causing detrimental effects by partitioning into air, water and soil phases (Roy, 2014). Majority of solvent waste is incinerated rather

than recycled. This in turn produces emissions and a further necessity of virgin solvent for future synthesis processes (Yaseen et al, 2021).

The 12 principles of green chemistry (Table 1) outline the idea of utilising less harmful and benign solvents in the formulation of less hazardous chemical synthesis, which are core principles in regard to solvents and their use (Anastas and Warner, 1998). Alternatives to traditional solvents which are safer and greener options found in literature include the use of water, supercritical fluids, ionic liquids and less environmentally hazardous solvents (Anastas and Warner, 1998; Kar et al, 2022).

Water is considered a green solvent having minimal hazards due to its inflammable, non-toxic and physico-chemical properties (Cvjetko Bubalo et al, 2014; Draye et al, 2020; Yaseen et al 2021; Kar et al, 2022). It is also a cheap and easily available solvent (Bubalo et al, 2014; Draye et al, 2020; Yaseen et al 2021). Water has various uses in industry as a cleaning agent, solvent for extraction of highly polar agents due to its polarity, and as a diluent.

Supercritical fluids are established green solvents having relatively high densities and properties similar to liquids and concurrently low viscosities and high diffusivities similar to gases (Sanni & Mutta, 2015; Clarke *et al,* 2018). Supercritical fluids are environmentally and economically feasible green solvents due to their ability to be recovered, recycled and reused without added purification steps and low energy consumption during operations (Knez et al, 2014). Most utilised supercritical fluids include supercritical CO_2 and supercritical water (Knez et al, 2014). Industrial applications of supercritical CO_2 include extraction processes, polymerization and catalysis (Knez et al, 2014; Clarke et al*,* 2018; Cseri et al, 2018). A notable application of

supercritical CO_2 as a greener alternative to organic solvent extraction is the extraction of cannabinoids from the cannabis plant (Ramirez et al, 2019).

Ionic liquids are organic salts that are composed of an organic cation and inorganic or organic anions with diverse structural possibilities which can alter the ionic liquids properties (Clarke et al, 2018; Faisal & Saeed, 2020; Haque et al, 2021). These have a long shelf life, high enthalpies of vaporisation therefore making them highly stable and non-volatile (Clarke et al, 2018; Faisal & Saeed, 2020; Haque et al, 2021). These factors as well the ability to solubilise organic compounds and metal salts makes ionic liquids an innovative green solvent which may be used as an alternative to conventional use of organic solvents (Gazal et al, 2021).

The 3rd principle of green chemistry coined by Anastas and Warner in 1998 states that, when possible, "synthetic methodologies should be designed to use and generate substances which possess little or no toxicity to human health and the environment". Following the establishment of the concept of green chemistry and the growing concern of environmental sustainability, major pharma companies such as GSK have continuously developed solvent selection guides (Jimenez-Gonzalez et al, 2004). These guides aid researchers in making sustainable, informed decisions when choosing solvents at the research and development phase for pharmaceuticals manufacturing (Jimenez-Gonzalez et al, 2004; Clark et al, 2018). Various solvent selection guides, tables and tools are available such as the proprietary GSK solvent sustainability guides (Slater & Savelski, 2007; Alder et al, 2016), BMS Process Greenness Scorecard (Slater & Savelski, 2007), publicly available American Chemical Society's Green Chemical Institute (ACS GCI) Pharmaceutical roundtable solvent selection guide and Innovative Medicines Initiative CHEM-21 (McElroy et al, 2015; Prat et al, 2016) amongst others (Slater & Savelski,

2007).[7] According to the assigned score per criteria, a traffic light colour system is commonly used to easily indicate a solvent with less known issues in comparison with one with more known issues (McElroy et al, 2015; Clarke et al, 2018).[7]

At times the need to use organic solvents is inevitable due to parameters such as solubility. Despite the necessity of such solvents, other considerations such as solvent recovery and recycling may be incorporated within a synthesis process for reuse of the solvent (Slater et al, 2010; Savelski et al, 2017; Cseri et al, 2018). Solvent recovery and reuse may offer an economic advantage to incineration as it reduces purchase of the virgin solvent, storage, transportation and waste costs while having an environmental benefit of reducing waste and greenhouse gas emissions (Kim et al, 2014; Savelski et al, 2017; Cseri et al, 2018). Despite this, major limitations include issues relating to ease of separation of mixtures which tend to be more difficult if mixtures have similar boiling points, energy requirements in recovery processes and meeting necessary regulations (Lapkin et al, 2009; Slater et al, 2010; Savelski et al, 2017; Cseri et al, 2018). Methods of solvent recovery utilised include distillation, adsorption and membrane filtration processing such as organic solvent nanofiltration (Kim et al, 2014; Cseri et al, 2018; Han et al, 2022).

The ideal strategy regarding use of solvents in the synthesis of the product would be opting a benign by design pathway. This is a process that incorporates strategies as mentioned above, one which utilises less solvents or eliminates the use of solvents (Draye et al, 2020). Use of catalysts and non-classical energy routes such as ultrasound,

[7] ACS GCI Pharmaceutical Roundtable Solvent Selection Guide Version 2.0 Issued [Internet]. 2011.[cited 2024 Jul25] Available from: https://www.acs.org/content/dam/acsorg/greenchemistry/industriainnovation/roundtable/acs-gci-pr-solvent-selection-guide.pdf

microwave or mechanochemical process are methods of reducing or eliminating the need for solvents (Sanni & Mutta, 2014).

3.1.2 Wastewater treatment systems

The wastewater content produced by the pharmaceutical industry is complex, mainly consisting of organic matter, slow biodegradability matter, toxic compounds such as antibiotics and other APIs (Guo et al, 2017). The concentrations present depend on the operations carried out within the plant, such as washing of equipment or extraction (Gadipelly et al, 2014). Wastewater treatment systems improve the quality of wastewater emitted into the environment. These treatment systems can be classified into conventional treatment processes which are generally used as a primary treatment, and advanced treatment processes which have a higher efficacy of removing pollutants from water (Gadipelly et al, 2014; Angelakis & Snyder, 2015). Different techniques in which pharmaceuticals and other contaminants can be removed from wastewater include adsorption, biological processes and chemical advanced oxidation processes (Karunganye, 2020).

Biological treatments employing aerobic and anaerobic processes are the conventional methods commonly used within the pharmaceutical industry to treat process wastewater (Gadipelly et al, 2014). The conventional activated sludge process is an example of an aerobic process applied globally due to being relatively low-cost and effective as a primary treatment (Jelic´ et al, 2012; Gadipelly et al, 2014).

Advanced treatment processes are subcategorised into advanced oxidation processes, which rely on hydroxyl reactions utilising photolysis and ozonation, and membrane

filtration processes such as ultrafiltration and reverse osmosis (Wang & Xu, 2012; Guo et al, 2017). Ozonation, photolysis, photocatalysis, and electrochemical oxidation are amongst some of the advanced oxidation processes which have a higher efficacy of removing pollutants from water than conventional techniques (Wang & Xu, 2012). Membrane bioreactors (MBR) combine conventional activated sludge and advanced membrane filtration methods (Al-Asheh et al, 2021). Their efficiency and improved retention of pollutants has made membrane bioreactors a preferred method compared to activated sludge processes (López-Fernández et al, 2012). This has also resulted in integrated MBR models incorporating other advanced treatment methods such as ozonation-anaerobic MBR (Kaya et al, 2017; Wang et al, 2018). As noted by Guo et al (2017), the rational use of advanced techniques can improve the quality of wastewater emitted into the environment, thereby reducing the environmental impact.

3.1.3 Renewable energy and energy efficiency

Majority of daily and industrial activities are reliant on the use of fossil fuels as an energy source resulting in tons of CO_2 being released as an air pollutant (Rypkema, 2018).[8] Apart from the environmental impact, fossil fuel stores are finite (Rypkema, 2018). The implication is such that if an alternative source of energy is not captured, future generations may not have a source of energy (Rypkema, 2018; Opeyemi, 2021). Renewable energy is an alternative energy to fossil fuels, which is abundant and derived from natural sources such as solar, biofuels and biomass which are more sustainable options (Chen, 2017; Guney, 2019; Opeyemi 2021).

[8] Health Care Without Harm. Health Care's Climate Footprint [Internet]. 2019 [cited 2024 Jul 25]. Available from: https://noharm-europe.org/content/global/health-care-climate-footprint-report

Solar energy has been used in facilities as an alternative to fossil fuels for heat and electricity generation such as by Ram Pharma in Jordan (Haagen et al, 2015; de Sá et al, 2018; Frein et al, 2018). The Direct Steam Generation system used supplies steam for process heat and air conditioning providing a cleaner method of energy generation (Frein et al, 2018). In comparison to solar energy, biofuels such as methanol and ethanol, obtained through combustion of plants and biomass, are cleaner alternatives to fossil fuels however these still have a relatively higher carbon footprint (Rypkema, 2018).

In a study conducted by Azzopardi (2020), different methods of increasing energy efficiency in a local pharmaceutical manufacturing plant included (i) the use of LED bulbs and motion sensors, (ii) inspections and changing insulation of heating, ventilation and air conditioning (HVAC) systems and heating pipework, (iii) proper fittings to reduce duct leakages for HVAC systems and (iv) timely maintenance such as of air handling unit filters. Other suggested projects included the introduction of solar photovoltaic panels and decommissioning inefficient equipment such as boilers and dehumidifiers (Azzopardi, 2020).

Fuel cells are electrochemical devices by which electrical energy is produced via a chemical reaction (Lucia, 2014; Xu et al, 2017). The fuel cell consists of an electrolyte in contact with an anode and cathode by which the fuel is oxidized on the anode, releasing protons which are transported through the electrolyte to the cathode and electrons which flow to an external circuit under an electrical potential (Xu et al, 2017). Fuel cells are currently being studied for long-term commercial use as alternatives to combustion engines and boilers which provide cleaner energy by decreasing greenhouse gas emissions (Sahajwalla, 2018). Other advantages include the variety of fuels which do not include fossil fuels such as hydrogen, methanol and ethanol (Lucia, 2014; Xu et al, 2017).

3.1.4 Green chemistry

The 12 principles of green chemistry (Table 1) focus on creating a benign process to decrease waste production at the source rather than resorting to treatment later (Anastas & Warner, 1998; Sharma et al, 2020). In essence, the aforementioned applications used within the manufacturing industry are based on the green chemistry principles.

3.1.4.1 Green metrics

Green metrics are used within the pharmaceutical and chemical industry as a means of measuring the environmental impact of chemical processes (Tobiszewski et al, 2015).

While selective synthetic methods have been at the forefront of chemical engineering and API manufacturing, Barry M. Trost in 1991 was one of the first to question process efficiency in terms of how much reactant is utilised within a process, which he referred to as atom economy. The atom economy calculation is a broader representation of efficiency in terms of reactant in final product. Atom economy may be calculated by dividing the molecular weight of the desired product by the total sum of the molecular weights of all reagents utilised within a stoichiometric equation (Calvo-Flores, 2009; Wang et al, 2011). The greater the atom economy value, the greater percentage that all reactants are utilised and are present within the final product (Calvo-Flores, 2009; Wang et al, 2011). Similarly, reaction mass efficiency gives a measure of the efficiency of a process, however giving a broader utilisation of reactants (McElroy et al, 2015).

Other mass efficiency metrics include mass intensity for a single step as well as process mass intensity for an entire process (Sheldon, 2018). These metrics are a measure of the total mass of materials used to produce a given mass of product (Tobiszewski et al, 2015).

All mass-based inputs including solvents, catalysts and reagents are included within the mass intensity metric in addition to yield and stoichiometry (McElroy et al, 2015). Other useful mass indicators include solvent intensity and waste intensity (Constable et al, 2008). Percentage yield is a frequently used metric as a measure of success and efficiency of the process (McElroy et al, 2015). Percentage yield is especially taken into consideration in the scalability of chemical processes (Constable et al, 2008). Environmental footprint metrics are another type of indicator used to measure the environmental impact of the supply chain. Such examples include carbon footprint, water footprint and energy consumption (Sheldon, 2018). This gives a measure of greenhouse gases included CO_2 produced, the amount of water used, and energy use respectively (Matustík & Kocí, 2021).

3.1.4.2. Flow production

Batch processing is the conventional method of manufacturing consisting of a sequence of steps in which groups or amount of product go through the same steps at the same time (Schaber et al, 2011). Continuous flow manufacturing is characterised by the continuous input and output within a process. Continuous flow manufacturing is gaining popularity due to the prospect of decreasing production costs while improving product quality as well as having an environmental advantage (Schaber et al, 2011; Rodgers & Jenson, 2019). These environmental advantages and green chemistry principles applications include minimal byproduct formation therefore improved atom economy, reduced solvent volume required and reduced energy requirements (Burhcam et al, 2018; Wang & Lakerveld, 2018; Rodgers & Jenson 2019).

3.1.4.3 Synthesis processing

One pot synthesis is another green chemistry approach by which isolation and purification steps for intermediates are eliminated (Ngo et al, 2014; Hayashi, 2016). This therefore reduces solvent necessity and use, waste production and increases reaction efficiency (Ngo et al, 2014; Hayashi, 2016).

3.2 Structured interviews

16 companies were identified as manufacturing facilities relevant for inclusion in this study. A total of seven manufacturing sites consisting of one API, five FDF and one MC site agreed to participate in this study (Table 2). Classified according to the definition by EU recommendation 2003/361/EC, two small, three medium and two large enterprises participated in this study.[3] Small enterprises are at the time of interview single dose facilities while the other enterprises produced multiple different products per year ranging from small molecule generics (n=4) to injectables (n=1).

Table 2: Company Demographics of Participating Companies

Industry type		API	FDF	MC
Number of Respondents		1	5	1
Company size	Small Enterprise	0	1	1
	Medium Enterprise	1	2	0
	Large Enterprise	0	2	0

3.2.1 Structured interview findings

Structured interviews were held over the time period of 1 year starting from April 2023 to March 2024.

3.2.1.1 Pharmaceutics in the environment

Due to increased awareness and studies relating to the increasing pharmaceutical concentrations within the environment, respondents were questioned if they were concerned about this. While three respondents stated that it was a concern, four respondents stated that this was not. Regulations set in place by authorities, such as the Environment and Resources Authority which require reports about emissions (n=1) and measures implemented within processes to protect the environment, where reasons why respondents where not concerned (n=1). The concern of other respondents was mainly related to pharmaceuticals in water which may be let out into drain systems (n=2) with one of these companies adopting dry wiping techniques before cleaning processes to reduce pharmaceutical effluents.

3.2.1.2 Green pharmaceutical practices

Respondents were questioned if they had ever heard the term green pharmaceutical practices, of which five stated they had, while the others stated they had not and were not aware of what it entails. When questioned from where they had heard the term, responses included that their field of study during university was based on green chemistry and green practices (n=2), student interviews (n=1) and articles (n=2).

The financial aspect of implementing green practices was noted as a major barrier and challenge (n=4). A second challenge noted included the regulatory aspect (n=3) whereby there is a difficulty in making changes to processes which have taken a number of years to be approved. A third challenge noted was that the manufacturing industrial process is a challenge in itself (n=2). Industrial processes are carried out at large scale and utilising the conventional methods is at times easier and more cost effective.

Respondents were questioned on the green pharmaceutical practices implemented within the facility. The API manufacturing site was noted to implement WWTS, green solvents, solvent recovery, one pot synthesis and environmental assessment methods (Fig. 2). Green practices implemented at FDF manufacturing included environmental assessment methods (n=2), renewable energy (n=2), paperless approach (n=3) and WWTS (n=1) (Fig.2). Regarding the MC facility, main activities included extraction of the cannabinoids of which CO_2 rather than organic solvents is used (Fig. 2).

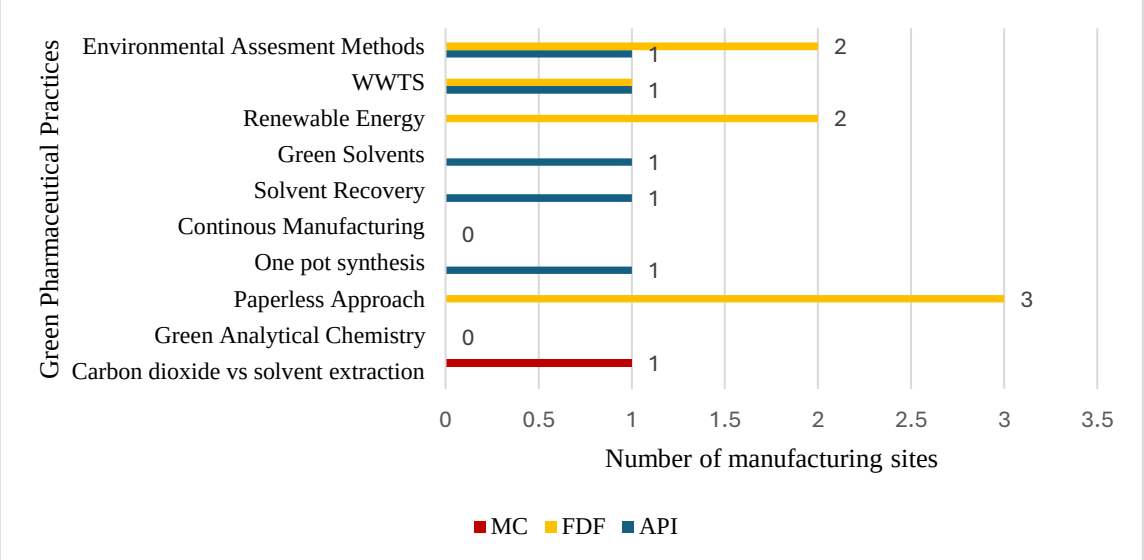

Figure 2: API (N=1), FDF (N=5) and MC (N=1) manufacturing sites applying green pharmaceutical practices locally

Environmental assessment methods utilised by the 2 FDF and API facility included measuring energy consumption (n=3), water use (n=2), waste generated (n=1) and CO_2 emissions (n=2). Companies which did not state to apply environmental assessment methods were questioned if there were plans for implementation in the future. While three companies agreed to having plans, one company stated it would only consider implementation if the prospect was financially beneficial. When questioned about reasons why environmental assessments methods where not applied, the financial aspect was noted as a limitation for application (n=2) and that there is a lack of knowledge of what green metrics and environmental assessment methods are, making incorporation into a procedure difficult to defend to management (n=1). Despite this, process metrics such as yield where noted to be utilised by two companies, mainly to understand the efficiency of a process.

Solar energy was the renewable energy method stated to be utilised (n=2). Reasons why companies do not utilise renewable energy sources such as solar energy included lack of roof space (n=2), large initial investment required (n=5) and future expansion projects (n=2). Despite this, three companies stated that they intend solar panels to be installed in the future.

While the API manufacturing site evaluates solvent environmental impact during solvent selection, this is not considered in the FDF and MC manufacturing sites since research and development establish solvents to use (n=6) and solvents such as alcohols and water only are used in established cleaning processes (n=4). Solvent recovery is only a practice utilised by the API manufacturing site. These solvents, including acetone, butanone and ethyl acetate, are transported for recovery via distillation. The minimal use of solvents

(n=4) by the FDF and MC manufacturing site was noted as a reason as to why this practice is not implemented.

Advantages to the introduction of a paperless approach included the ease and efficiency in finding documents (n=2). The four respondents which do not yet implement a paperless approach do intend to do so in the future.

3.2.1.3 Pharmaceutical waste

Regarding the WWTS utilised, conventional wastewater treatment methods using physicochemical methods such as flocculation (n=1) and grease traps (n=1) were noted.

Various waste types were noted to be generated in the facilities including hazardous/cytotoxic waste, solvent waste, solid reject waste, contaminated packaging, personal protective equipment and spent biomass The method of disposal of this pharmaceutical waste included exportation for incineration (n=6) as there is no local incineration site. The API manufacturing site does not send all solvent waste produced for incineration but also sends solvent waste for recovery via distillation.

Waste minimisation efforts and suggestions on how to reduce pharmaceutical waste within the industry made by respondents included solid waste reduction (n=4), reduction of rejects (n=2), reuse of water for office building use (n=2), paperless systems (n=2), and dry wiping practices (n=1).

Respondents were questioned on their opinion on the reduction of packaging size and how it would affect the manufacturing industry. The opinion of four respondents was that although one problem of reducing pharmaceutical waste may be reduced, another problem such as increased outer packaging waste is created as more plastic and other

materials would be required to create packs with less medication within. Solutions brought forward included the use of bottles rather than blister packaging which is harder to recycle due to the mix of plastic and metal foil (n=2) as well as rather than reducing the pack size, the empty air space within containers and packaging should be optimised (n=2). The explanation of such a suggestion was that optimising the configuration within the packaging can allow for more products to be shipped per unit space. Implication to the manufacturing industry of such directives being introduced included having regulatory and contract implications since packaging specifics such as the number of tablets within a box and the outer packaging are dictated within the medication's dossier (n=2). Another implication was that if pack size was to be reduced, this could potentially increase costs for the manufacturers as well as for the patients purchasing the medication (n=2).

3.2.1.4 Revision of GMP's

Directive 2003/94/EC sets principles and guidelines of GMP's in relation to medicinal products for human medicine.[9] Currently GMP's published by the European Medicines Agency do not cover the control of emissions of pharmaceutical products and residues into the environment. Respondents were questioned on their opinion whether GMP's outlining standards for discharge of pharmaceutical residues into the environment should be a necessary inclusion. While one participant was in agreement, the other six respondents disagreed. The consensus was that such an inclusion would be out of the

[9] European Commission. Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use [Internet]. Official Journal of the European Union. 2003 [Cited 2024 Jul 25]. From: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32003L0094

scope and conflicting with the purpose of GMP's (n=6) and that it should be an issue managed by other entities such as by the Environment and Resource Authority (n=4). A suggestion made for those within the manufacturing industry which are more environmentally conscious and require tools to manage their environmental responsibility included aids such as ISO 1400, an optional standard which sets out criteria for environmental management.

The implication of introducing such GMP's on the company was sought. From the seven respondents, two stated that such changes to GMP's would have a minor impact, with a reason given by one respondent being that they are compliant with all current regulations and guidelines but changes to be complaint may be devastating for others. Cost was the stumbling block expressed by three respondents. The increase in workload due to having to review processes (n=1), the general increase in tasks of testing (n=2) as well as the limitation of resources and expertise in the field (n=2) was noted. The length of time needed to comply was an issue brought forward (n=2) whereby a long period of time would be required for companies to adapt and implement changes.

3.2.1.5 Procurement of raw materials and API's

China and India are amongst the biggest manufacturers of API's and raw materials globally. It was questioned whether the EU should impose quality marks for pollution control on these materials manufactured outside of Europe as they are a major import for the EU (Milmo, 2017). The five respondents which were in agreement were representatives from the FDF facility. The API facility and one FDF facility did not agree with the statement. The main concern of the FDF facility, also characterised as a small enterprise, was that this would increase the cost of production. The API facility stated that

similar concepts are applied on an individual and private bases, such as forming part of certain platforms such as EcoVadis, in order to align with objectives of outside contractors.

3.2.1.6 Environmental risk assessment and benefit to risk assessment

While the ERA takes into account the risks associated with the use and disposal of pharmaceutical products, risks associated with manufacturing is not a criterion necessary in the documentation for a marketing authorisation (Larsson, 2014).[10] Stakeholders were questioned on whether a gradual inclusion regarding environmental risks and burden of a drug during manufacturing rather than only on the use of the product should be included in the environmental risk assessment of a product. All respondents were in agreement to such a proposal.

Respondents were further questioned whether the ERA should constitute as a criterion for refusal of the marketing authorisation if the impact on the environment is considered substantial. Four respondents agreed to the above statement while three disagreed. Reasons included that a risk-benefit assessment for the outcome to patient health in relation to the environmental impact is required (n=2) and that human health and the potential of medication aiding in this is of greater importance (n=1).

Regarding the issue of whether the environmental risks of a medicinal product should be part of the products pharmacovigilance, five respondents agreed with the sentiment of one of the respondents being that awareness to environmental impact is always beneficial.

[10] European Medical Agency, Committee for medicinal products for human use. Guideline on the environmental risk assessment of medicinal products for human use - draft. [Internet]. 2024[Cited 2024 Jul 26]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1_en.pdf

A Likert scale was used to gauge the respondent's opinion of how effective and feasible the introduction of ERA regulations would be in the ability to decrease pharmaceuticals within the environment. Respondents were requested to give a score between one and five with one being that in their opinion the above was not at all effective or feasible and five being that in their opinion the above was extremely effective and feasible (Table 3).

Table 3: Response of participants (N=7) in relation to effectiveness and feasibility of ERA in decreasing pharmaceuticals within the environment

	1 Not at all	2 Slightly	3 Moderate	4 Very	5 Extremely
Effectiveness of ERA in decreasing pharmaceuticals in the environment	0	3	1	3	0
Feasibility of ERA in decreasing pharmaceuticals in the environment	1	1	3	1	0

3.2.1.7 Willingness to pay

Stakeholders were questioned on whether the company would be willing to pay a fee to aid in research regarding green initiatives and provide educational campaigns. It was noted that respondents who stated that the company would not be willing to pay were those identified as being small enterprises (n=2) while those that stated they were willing to pay were those identified as being medium and large enterprises. Five respondents stated that they would be willing to donate. Situations in which they would be willing to

do so included through collaborations or donations to universities to engage and aid in research (n=3).

The opinion of stakeholders was sought on whether a fee on medications to the public such that this would contribute to funding green initiatives and having information on the environmental impact of the medicinal product more available should be introduced. One participant stated that they would be willing to pay and in favour of such an introduction. Respondents noted the fact that medications are already costly and introduction of such an initiative would place added constraint on the paying patient (n=3). Responsibilities of local government was mentioned, namely it's responsibility to educate the population on environmental impact and waste rather than the pharmaceutical industry having such a role (n=1). Issues on who should pay such a fee and if the local government should sustain an amount of the fee was brought up by two respondents.

3.2.1.8 Incentives and fines

Lastly, what are the main incentives to adopting green practices was questioned. Financial gain (n=3) was a major defining factor for which companies would be incentivized to adopt green practices. Regulatory authorities and legislation requiring one to abide by such regulations (n=2) was also identified as an incentive. The perspective of prospective clients of the company (n=2) was identified as an initiative to adopt green practices in order for the company to have a better image. Lastly the impact on the environment (n=3) was also considered an initiative especially to those who considered themselves environmentalists (n=2).

Respondents were questioned on their thoughts on whether more innovations would be developed to meet green ideals if incentives for companies striving to be greener were in place locally, such as a monetary prize. Examples given to stakeholders' efforts in being more sustainable included the development of greener, more sustainable drugs and investment in new WWTS. Six respondents agreed with the incorporation of such an incentive. The outlook however was that there would need to be a financial incentive (n=3).

A Likert scale was used to gauge the respondent's opinion on the introduction of fines on companies which do not implement green practices within manufacturing and which do not ensure safe emission levels of pharmaceuticals within the environment. Respondents were requested to give a score between one and five with one being that they strongly disagreed with the above and five being that they strongly agreed (Table 4).

Table 4: Response of participants (N=7) in relation to imposing fines

	1 Strongly Disagree	2 Disagree	3 Neutral	4 Agree	5 Strongly Agree
Imposing fines on pharma companies that do not implement green practices	0	2	0	3	3
Imposing fines on pharma companies that do not ensure safe emissions levels of pharmaceuticals	0	0	1	3	3

3.3 Scorecard Development

The concept for the design of the scorecard was to develop a simple, usable tool which can be utilised within the research and development phase of a manufacturing process so that chemists can easily identify areas of improvement. The scorecard was developed in such a way that each step of a synthesis process is accounted for including the work-up to the reaction such as any purification, distillation or filtration steps, the reaction itself and any cleaning processes. In this way each individual step can be looked at separately as well as a cohesive whole through the total sum.

3.3.1 Criteria for inclusion into tool

Currently utilised and novel methods of quantifying the greenness of a process were researched by conducting a literature review. Criteria to be included were those identified as having a major impact on the environment regarding the manufacturing process. This included raw materials, solvents used, energy consumption, cleaning processes and waste generation.

3.3.1.1 Raw Materials

A method of calculating a raw material score was devised to have an indication of the safety and environmental impact. Hazard classification methods identified included the HMIS and the GHS.[4,5] GHS was chosen in this study as it is a globally used classification system adopted by entities such as the United Nations and the EU.[4] On the other hand, the HMIS is a voluntary rating system which is mainly utilised with the United States.[5] To follow the standard used in the global trade of chemicals, the GHS was selected. This

hazard information is available from safety data sheets of the raw materials and from databases such as "PubChem".[6]

In the GHS hazard classification system, each hazard statement code is denoted with the letter H. The first number of the hazard statements indicates the hazard type, namely 2 refers to physical hazards, 3 indicates health hazards and 4 refers to environmental hazards. Using the GHS classification system, the individual raw material score is calculated according to the number of GHS hazard statements and whether the hazard statement includes the word 'Warning' or 'Danger' for which a penalty would be given.

The following equation [*Eq:1*] was formulated:

[Eq:1]

$$\textbf{\textit{Raw material score} = [(}\sum\textbf{\textit{Physical}} + \sum\textbf{\textit{Health}} + \sum\textbf{\textit{Environmental statements) x 1 (Warning)]} + \textbf{\textit{[(}}\sum\textbf{\textit{Physical}} + \sum\textbf{\textit{Health}} + \sum\textbf{\textit{Environmental statements) x 2 (Danger)]}}$$

An alternative method was also formulated in the situation that the GHS classification score is not available which is based on pictograms. In this method, the number of pictograms is multiplied by one if it includes the signal 'Warning' or multiplied by two if it includes the signal 'Danger'. This method was based on a similar concept utilised in the semi-quantitative tool named the Analytical Eco-Scale (Gałuszka et al, 2012).

3.3.1.2. Solvents

As mentioned previously solvents are the most commonly used agents within the industrial manufacturing processes. The choice of solvents can have a detrimental effect on the environment as well as the health and safety of workers as discussed in Chapter 3.1.1. Regarding the development of the scorecard, different solvent selection guides were identified through literature. Ones initially considered to form the basis of the solvent

score included the GSK solvent sustainability guide and the CHEM21 solvent selection guide developed through a collaboration between the EU innovative medicines initiative and CHEM21 initiative (Alder et al, 2016; Prate et al, 2018). In the CHEM21 solvent selection guide, solvents are ranked as recommended or preferred, problematic, hazardous and highly hazardous (Prat et al, 2018). This is based on the safety, health and environmental criteria. Similarly to the method utilised to calculate the raw material score in the study, the GHS classification system is utilised in the CHEM21 guide to calculate the safety, health and environmental criteria (Prat et al, 2018). In this study, the GSK solvent selection guide was used to calculate the solvent classification score.

The method to obtain the solvent classification was developed which included adding the scores for waste, environmental impact, health, flammability and reactivity of the solvent. Life cycle analysis (LCA) was not included in the summation. Following the focus group discussion, panellists brought forward the issue that LCA for the raw material score was not taken into consideration therefore should be eliminated regarding the solvent score to reduce bias in this regard. It was also noted that not all solvents listed within the guide had an LCA score. Through the focus group study, it was noted how certain criteria in their opinion are of more importance and relevance in terms of the objective of the scorecard. In their opinion, a greater weighting should be given to the environmental impact and health impact while a lesser weighting to waste should be given in the summation equation. The maximum possible solvent classification score according to the assigned weighting was calculated as being 100. Since within the developed scorecard a greater number depicts a less green process, and within the solvent selection guide a greater number depicts a greener solvent, the summation of the individual scores multiplied by their weighting deducted from the maximum possible solvent classification

score (100) was used to calculate the solvent classification score. The following equation [*Eq:2*] was developed:

Solvent Classification Score = [E*q:2*]
100 - [(Waste) x0.5 + (Environmental Impact + Health) x1.5 + flammability + reactivity]

An issue raised within the focus group discussion was the method of quantifying the amount of solvent used in proportion to how much final product is produced in the process. It was suggested that relative values comparing the solvent per unit mass produced be used rather than an absolute value. The method of calculating this was by utilising the equation for mass intensity. It was also suggested that a range system be used to assign penalty points which may be multiplied to the solvent classification score. The following equation [*Eq:3*] was used to calculate the solvent used (L) per mass produced (kg):

$$\textit{Mass Intensity} = \frac{\textit{Solvent Used}}{\textit{Total Mass Produced}} \qquad [Eq:3]$$

The ranges for assigning penalty points as suggested by panellists according to practical experience are presented in Table 5.

Table 5: Penalty point assigned to solvent used (L) per mass produced (kg)

Mass Intensity	Penalty Point
>10 L/kg product	1
10-15 L/kg product	2
15-20 L/kg product	3

The following equation [*Eq:4*] can then be used to calculate the solvent score:

Solvent Score= Solvent classification score x Mass Intensity Penalty point [*Eq:4*]

3.3.1.3 Energy consumption

Two methods were developed to calculate energy consumption. Method one is based on energy consumption in kWH per sample. Here penalty points are awarded accorded to what kWH range the process is in. This was adapted from the analytical eco-scale developed by Galuszka et al (2012). In discussions with experts in the field, the general sentiment was that such a method was complex, and that energy use may vary and be dependent on the industrial plant, batch size and type of reactor used such as stainless steel or glass lined. For this reason, method two was selected for the scorecard due to its practicality and simplicity. This similarly is based on penalty points which are awarded according to what temperature range the process is in. Ranges found in literature included mild conditions to be between 0°C to 70 °C, those outside mild conditions −20°C to 0°C and 70°C to 140 °C and those utilising the highest amount of energy with temperatures below -20°C and above 140°C (McElroy et al, 2015). Suggestions made by the panel consisted of changing these ranges such that anything below 0°C would be considered as utilising greater energy as any process requiring freezing temperatures are more energy intensive.

This resulted in temperature ranges as follows (Table 6):

Table 6: Penalty point assigned to temperature range

Temperature range	Penalty Point
20°C to 70 °C	1
0°C to 20°C and 70°C to 140 °C	2
Below 0°C and greater than 140 °C	3

To obtain the energy consumption of the process however, the length of time of a process required to be considered. Suggestions made by panellists based on practical experience were as follows (Table 7):

Table 7: Penalty point assigned to reaction time

Time of reaction	Penalty Point
≥5 hours	1
5 - 10 hours	2
10 - 24 hours	3
≤ 24hours	4

The multiplication of the temperature range penalty point, and the time of reaction penalty point would give a representation of the energy consumption score in the scorecard. This was developed so that one can distinguish between processes having long reaction times at high temperatures in comparison to those for shorter periods of time, which although a higher temperature therefore greater energy requirement is needed, still has a lesser energy consumption than the former.

3.3.1.4 Catalysis

A method of calculating the catalyst score in the developed scorecard included incorporating the elemental risk of depletion, recoverability and the efficiency of the catalyst. Similarly to McElroy's method of ranking critical elements at risk of depletion, the periodic table showing critical elements was used to rank catalysts containing critical elements depending on the remaining years until depletion of known reserves (Fig. 3). A penalty system based on the periodic table was devised (Table 8).

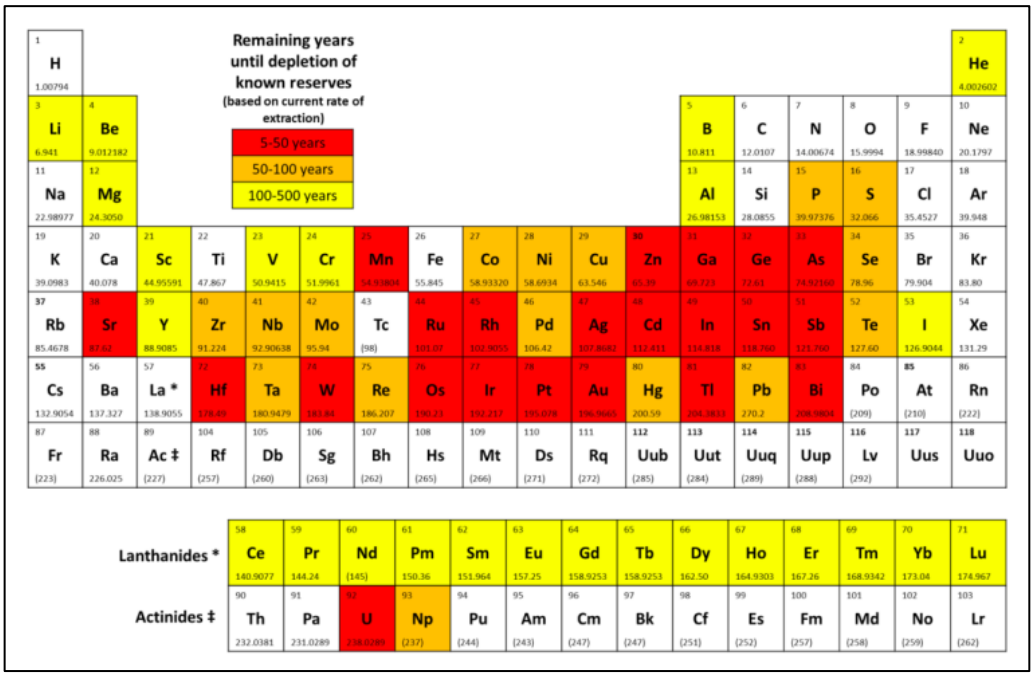

Figure 3: Periodic table depicting elements at risk of depletion

(Reproduced from: Hunt A, Farmer T, Clark J. Elemental sustainability and the importance of scare element recovery. In: Hunt A, editor. Element recovery and sustainability. 2013. p. 3)

Table 8: Penalty point assigned according to years remaining until depletion of known reserves

Years remaining until depletion of known reserves	Penalty Point
5-50 years	2
50-100 years	1
100-500 years	0

A penalty point system was also devised according to the recoverability of the catalyst. If catalyst used is not recovered within the process, a 2 point penalty would be assigned while no penalty point would be assigned if the catalyst is recovered or recycled.

The third aspect which was noted of importance through literature was the activity and efficiency of the catalyst. Catalytic activity is calculated in terms of turnover number or

turnover frequency, depending on the type of catalysis (homogenous, heterogenous or enzymatic) (Umpierre et al, 2011). When calculating the turnover number for enzymatic catalysis, Michaelis-Menton kinetics is used to calculate the maximum number of molecules that an enzyme can convert into a product per catalytic site (Umpierre et al, 2011). In terms of metallic catalysts, the turnover number is described as the number of moles of a limiting reagent that a mole of catalyst can convert before becoming inactivated (Umpierre et al,2011; Hodgson & Scaiano, 2018). The following equation [*Eq:*5] may be used to calculate the turnover number:

$$\textit{Turnover Number} = \frac{\textit{Moles of Limiting Reactant}}{\textit{Moles of Catalyst}} \times \textit{Yield} \qquad [Eq{:}5]$$

The greater the turnover number the longer the catalyst will retain its activity. To depict this in line with the scorecard where the greater the value, the less sustainable, the inverse of the turnover number used to portray the efficiency of the catalyst.

In this way the catalyst score may be calculated through the summation of the penalty points according to the years until depletion of known reserves, whether the catalyst is recovered and the efficiency. This will be calculated as follows:

$$\textit{Catalyst Score} = \textit{Elemental risk of depletion penalty point} + \textit{no recovery penalty point} + \frac{1}{\textit{Turnover number}} \qquad [Eq{:}6]$$

3.3.1.5. Cleaning

Cleaning processes are one of the methods of solvent waste generation within the pharmaceutical industry (Brems et al, 2013; Conception, 2019). Cleaning methods used

depends on the equipment as well as physical and chemical properties of the residue (Porter, 2011; Prabu et al, 2015). Different methods include mechanical action such as brushing, scrapping or use of pressurised water, dissolution through use of solubilising solvent, saponification, detergency and chemical reactions such as oxidation and hydrolysis reactions, mainly used to breakdown organic residue (Porter, 2011; Prabu et al, 2015). Water is a commonly used solvent in the cleaning and rinsing of equipment (Prabu et al, 2015). Routinely used cleaning solvents within the API manufacturing industry include methanol, acetone, dimethyl formamide and ethyl acetate which are usually able to solubilise the API and are readily available (Prabu et al, 2015; Joshi & Adhikari, 2019). To reduce risks of cross contamination and to ensure that equipment adheres to the validation requirements, multiple cycles are usually necessary, resulting in further discard of large amounts of solvents (Prabu et al, 2015).

For the above reasons, cleaning was considered an essential step of which the environmental impact should be able to be quantified. Regarding the cleaning score, the number of steps as well as the solvent classification score were considered. The solvent classification score [*Eq:2*] is calculated in the same manner as mentioned in Chapter 3.3.1.2. According to the solvent used, the solvent classification score is multiplied proportionally by the number of cleaning steps involving that particular solvent. In such a way, the cleaning score can be calculated in the below manner:

[*Eq:*7]

Cleaning Score per Solvent used = Solvent Classification Score x No. of steps involving solvent

3.3.1.6 Waste Generated

Creating a benign by design process therefore reducing process waste is a main concept in the principles of green chemistry and creating sustainable synthesis processes. Various parameters were noted as having relevance in terms of determining a waste generated score. The first consideration made included the type of waste generated. The Waste Framework Directive 2008/98/EC is the European legislation in regard to waste.[11] Within this document waste may be classified as absolute hazardous, mirror hazardous, mirror non-hazardous and non-hazardous.[17] This classification is based on the GHS classification system, alike what is being utilised in this study.[12] Another factor which was deemed important was the amount of waste generated of a particular type of waste. Thirdly, whether the waste was recovered or not was another factor which was of importance in determining the greenness of a process.

An issue raised within the focus group regarding waste was that a method to distinguish between aqueous and organic waste is necessary. This point was mentioned to obtain a clearer portrayal of which waste components are representing the particular score. Although the waste classification score may be able to interpret this as organic solvents are mainly considered as more hazardous in comparison to aqueous media, the consensus was that this would be better differentiated by calculating the waste score for aqueous and organic waste separately.

[11] European Parliament and Council of the European Union. Directive 2008/98/EC [Internet]. Official Journal of the European Union. 2008 [cited 2024 Aug 15]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32008L009

[12]European Commission. Commission notics on technical guidance on the classification of waste [internet]. Official Journal of the European Union. 2018 [cited 2024 Aug 15]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?toc=OJ:C:2018:124:TOC&uri=uriserv:OJ.C_.2018.124.01.0001.01.ENG

To calculate a score for the classification of waste type generated, a method based on the GHS classification score present within the safety data sheet of the waste product was utilised. This was calculated using the below equation [*Eq:*8]:

[*Eq:*8]

$$\textit{Waste type} = [(\sum \textit{Physical} + \sum \textit{Health} + \sum \textit{Environmental statements}) \times 1\ (\textit{Warning})] + [(\sum \textit{Physical} + \sum \textit{Health} + \sum \textit{Environmental statements}) \times 2\ (\textit{Danger})]$$

To determine the amount of waste generated, equations for waste intensity [*Eq:*9] and process mass intensity [*Eq:*10] were utilised to obtain the waste percentage generated. Using equations for waste intensity and process mass intensity, in this manner one would be able to understand the waste generated in comparison to the input. This was calculated for the total mass input aqueous and total mass organic respective to whether organic or aqueous waste was produced. The following equations found in literature were as follows (McElroy, 2015):

$$\textit{Waste Intensity (WI)} = \frac{\textit{Total waste produced}}{\textit{Total mass input}} \qquad [Eq:9]$$

$$\textit{Process Mass Intensity (PMI)} = \frac{\textit{Total mass in step}}{\textit{Product mass}} \qquad [Eq:10]$$

$$\textit{Waste \%} = \frac{\textit{Waste Intensity}}{\textit{Process Mass Intensity}} \times 100 \qquad [Eq:11]$$

Solvents are one of the main resources utilised and discarded within the manufacturing process. Waste recovery was a criteria identified as of importance. For this reason, a penalty point system was devised based on whether waste was recycled or not. If waste is not recovered within the process, a 2 point penalty would be assigned while no penalty point would be assigned if waste is recovered or recycled.

In this way, the waste generated for aqueous and organic media may be calculated accordingly through the summation of the waste classification score, the waste % and the penalty point assigned according to practices of waste recovery.

3.3.1.7 Other metrics

Yield and atom economy were noted as two metrics already commonly utilised by chemists in the manufacturing industry as a way of measuring the success and efficiency of a chemical process (Clarke et al, 2018). To ensure the practicality of the tool, these two metrics were included to understand both process efficiency as well as sustainability within one document through the previously mentioned criteria.

Yield [*Eq:12*] and atom economy [*Eq:13*] may be calculated from the equations below:

$$\textit{Yield \%} = \frac{\textit{Moles of product}}{\textit{Moles of limiting reactant}} \times 100 \qquad [Eq:12]$$

$$\textit{Atom Economy} = \frac{\textit{Molecular weight of product}}{\textit{Total molecular weight of reactants}} \times 100 \qquad [Eq:13]$$

3.3.1.8. Calculating the final score

To calculate the final score, the summation of the raw material score, energy consumption score, catalyst sore, solvent score, cleaning score and waste generated score amount to the total score per step. The addition of the individual total scores per step would allow for the quantification of the greenness of an entire process, based on the scorecard methodology designed in this study.

3.3.2 Tool Validation

3.3.2.1 Conventional versus green synthesis pathways

To verify that a greener process would in fact result in a lesser total score, conventional and green synthesis pathways for the same product were found in literature to be applied within the scorecard. Basoglu Ozdemir, et al (2018) discusses the use of microwave-assisted synthesis as a method for greener piperazine-azole-fluoroquinolone based 1,2,4-triazole derivative synthesis. In the study, an experimental procedure was carried out to evaluate the yield and activity of the microwave-assisted green synthesis method in comparison to the conventional method. Available values present within the study were used to evaluate the scorecard developed. Values for amount of product produced, waste type, waste produced, and cleaning were not available.

The greenness assessment tool was utilised with values found in literature inputted such that in Appendix 5 the conventional synthesis pathway for piperazine-azole-fluoroquinolone based 1,2,4-triazole derivatives is portrayed while in Appendix 6 the scores for the greener synthesis pathway for piperazine-azole-fluoroquinolone based 1,2,4-triazole derivatives is portrayed (Basoglu Ozdemir et al, 2018). The total score for the conventional and green synthesis pathway was 2166.1 and 2152.5 respectively. Using the scorecard, one can indicate that the green synthesis pathway is in fact more sustainable due to the lower score obtained. Despite this, the difference between the two is not substantial as the main difference in the process work-up was the use of microwave irradiation over traditional reactors with limited difference in reagents. The time needed when using the microwave assisted method was far less, usually minutes, compared to the hours necessary when using the conventional reactor. This difference within the scorecard was not emphasised as the time range for the penalty point assigned to the

reaction time is in hours with the lowest range being ≥5 hours (Table 7). Therefore, a process of 10 minutes and 5 hours would have the same penalty point although there is a comparatively large difference in reaction time. Despite this, the main aspect by which the greener synthesis pathway is more sustainable is in terms of the energy consumption score, due to the reduced time and temperature required for the reaction, which is still clearly presented in the scorecard (Appendix 5 & 6).

Another factor which may have impacted the scorecard result are the values which are not available such as the amount of solvent used, type of waste, cleaning processes which are generally outlined within company manufacturing processes however not outlined within the experimental procedure. Thirdly, the fact that particulars for processes such as evaporation, crystallisation and distillation where not outlined also provides a gap in the data to enter within the scorecard.

Similarly, a green and conventional method for the synthesis of N-substituted pyrrole derivatives from furans was applied within the scorecard (Clauson-Kaas & Tyle, 1952; Khammas et al, 2018). The conventional method based on the Clauson-Kaas methoxylation of furans reaction was used (Clauson-Kaas & Tyle, 1952). The solvent-free method of synthesis of n-substituted pyrrole derivates using silica sulfuric acid catalysis was used as the green synthesis method (Khammas et al, 2018). This method was chosen due to being solvent-free as well as having a short reaction time which meets green chemistry requirements (Khammas et al, 2018). The end products of the two synthesis pathways are not identical since the conventional method synthesises 1-phenyl-2-(acetamidomethyl)-pyrrole while the green method synthesis produced different pyrroles according to the amine component. The example using 2-aminiobutan-1-ol was used in this exercise in relation to the green synthesis method (Khammas et al, 2018).

These synthesis pathways were selected since the end product is an N-substituted pyrrole derivative and the green synthesis method is based on the Clauson-Kass synthesis pathway.

The total score for the conventional and green method obtained when using the scorecard was 335.62 and 163.95 respectively. Using the developed scorecard one can easily distinguish how the use of solvents as well as solvent relative amount has a great effect on the total score (Appendix 7 & 8). For both methods, particulars regarding processes such as crystallisation, evaporation and distillation where not included since these were not provided within the respective studies. Information regarding cleaning processes and waste were also not present.

3.3.2.2 Pilot study

A pilot study was conducted using a decommissioned manufacturing process of which the basic operations of the production of the final product X was used (Appendix 9). This consisted of four synthetic pathways, synthesising three intermediates and the final product X. All process parameters are outlined including purging of the reactor, mass of reactants added, solvents and their quantities, time of heating, cooling and stirring at particular temperatures, cleaning processes as well as distillation and filtration processes.

In regard to waste generated, not all information is present. The exact nature of the waste, the amount and type of waste is not outlined. It has been assumed that any solvent used for cleaning is discarded since the only purpose is to clean the vessel or product and does not form part of the reaction. The only inputted values for waste type and amount were based on the above assumption of the cleaning solvents, or when clearly specified. In the

basic operations of the production of product X, the term ‘discard’ is utilised therefore it is assumed that this waste product will not be recovered.

The values in the scorecard are inputted in a step-by step manner for each product of each pathway (Appendix 9). Some steps such as stirring, heating and cooling are inserted within the same step. By inputting the values in this manner, one is able to decipher which part of the synthesis pathway is less green due to the higher score noted. Synthesis pathway A resulted in a total score of 230.02, pathway B 411.58, pathway C 556.34 and pathway D 293.84 respectively. It can be noted that the score is greater according to the number of steps per pathway but is also related to the number of cleaning steps and solvent used.

Chapter 4

Discussion

The outcome of this study has provided the opinion and knowledge of stakeholders within the local pharmaceutical manufacturing industry as well as those green pharmaceutical practices applied. It also gives light to prospective plans as well as current challenges within the local scenario. Through the development of the scorecard, a method of quantifying the greenness of a process as well as the ability to compare different parameters of a process has been developed.

4.1 Structured interviews

4.1.1 Pharmaceuticals within the environment

While pharmaceuticals within the environment are of increasing concern, for most of the respondents this was not. Reasons for this were since there are controls put in place within the manufacturing industry and regulations which need to be adhered to in terms of effluents in wastewater. This is in contrast with the opinion obtained in structured interviews conducted by Doerr-MacEwen et al, (2006) of which majority of respondents were concerned about the human and ecosystem health concerns from pharmaceuticals within the environment. Efforts however are still made by the industry. The respondent stating that pharmaceutical environmental pollution is a concern also mentioned that the company is in alignment with the Antimicrobial Resistance Industry Alliance. This alliance is a private sector coalition which provides sustainable solutions to push towards decreasing pharmaceutical concentrations, in particular antimicrobial products.[13] While improving antimicrobial resistance stewardship requires action at a community level, ensuring responsible antibiotic manufacturing is a step the industry can make to

[13] Why the AMR Industry Alliance? [Internet]. AMR Industry Alliance. [cited 2024 Aug 20]. Available from: https://www.amrindustryalliance.org/why-the-amr-industry-alliance/

minimizing the potential impact of pharmaceutical manufacturing on the spread of antimicrobial resistance by decreasing pharmaceuticals within the environment (Tell et al, 2019).

4.1.2 Challenges and barriers

Although it is evident that majority of respondents are aware of green pharmaceutical practices, these practices application within the industry is limited. The main barriers and challenges noted by respondents included the financial and regulatory aspect. While green practices are commonly regarded as being more cost effective, the initial investment and the necessity for an immediate return of investment was observed as a challenge. Regulations in place in terms of marketing authorisation of the product also limit the ability for making sustainable changes. A hurdle noted which impacted the application of more sustainable methods was whether processes were developed locally on site or not. International companies having development instruction from the mother company or third-party customer were noted to be less flexible in terms of sustainability.

4.1.3 Incentives, fines and ability to fund

Despite the financial and regulatory aspect being considered challenges, these were also identified as incentives to respondents. The prospective financial gain from introduction of green practices was one reason for incentivising applications. Similarly, the image of the company to be considered more environmentally friendly and sustainable from a client perspective was deemed a motivational point for green pharmaceutical practices applications. These incentives identified are similar to those mentioned by Veleva & Berkley (2017) who highlighted drivers for incorporating green chemistry principles

namely cost savings, improved reputation, legislation and customer demands which may lead to market exclusion if there is not a commitment to apply environmentally friendly practices.

In a study conducted by Alajarvi et al (2022), the willingness to pay by the public for the implementation of an environmentally friendly pharmaceutical policy in Finland was evaluated. It was established that persons who described themselves as being pro-environmentally friendly or environmentally inclined were more willing to pay to implement such policies. In this study, stakeholders were questioned on their opinion of introducing such a fee on medications to the public such that this would contribute to funding green initiatives and having information on the environmental impact of the medicinal product more available. Those companies identified as small enterprises were less willing to pay a fee to aid in research regarding green initiatives and provide educational campaigns. Company size was identified as having an influence on the ability to fund and incentivize the application of green practices.

4.1.5 Packaging size

Reduction and optimisation of packaging size is another current issue which is being discussed at an international level in the 'European Union Strategic Approach to Pharmaceuticals in the Environment'.[14] This directive is intended for the purpose of reducing pharmaceutical waste from unused medications. Despite take-back schemes for unused medications, disposal in drains and household trash is still a disposal route used for excess or expired medications in many countries, Malta being amongst these countries

[14] European Commission. European Union Strategic Approach to Pharmaceuticals in the Environment. [Internet]. Official Journal of the European Union. 2019 [Cited 2024 Jul 25]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1552310298826&uri=COM:2019:128:FIN

(Paut Kusturica et al, 2016; Smale et al, 2021). While waste disposal management is one way of ensuring appropriate disposal and reduction of pharmaceuticals within the environment, reducing the possibility of excess unused medication is a more sustainable option (Smale et al, 2021). Medication package size commonly deviates from the appropriate dose and quantity required for treatment (Bekker et al, 2018; Smale et al, 2021). It is one way in which patients may end up with excess. Having a variety of package sizes according to the usual dosage regimen is a method by which excess may be reduced (Smale et al, 2021).

4.1.5 Environmental risk assessment

While gathering a picture of the green practices applied within the facility was an objective of the study, the opinions of the stakeholders was also sought pertaining to current issues being discussed at an international level, specifically the ERA. As per Directive 2001/83/EC Article 8 (3), assessment of the undesired effects on the environment and potential risks on exposure of the medicinal product is required during the application for a marketing authorisation (Kuster & Adler, 2014).[15] Currently issues pertaining to the ERA are being discussed at length at an international level within the EU and a new revision of guidelines which takes effect on September 1st 2024 has been released.[14] Respondents were overwhelmingly in agreement to the gradual inclusion of environmental risks and burden of a drug during manufacturing rather than only on the use of the product to be included in the environmental risk assessment. This is of particular importance since the ERA as highlighted by Caneva et al (2014) is at times not

[15] European Commission. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [Internet]. Official Journal of the European Union. 2001 [cited 2024 Jul 26]. Available from: https://eur-lex.europa.eu/legalcontent/en/ALL/?uri=CELEX%3A32001L0083

considered a priority as 37% of the responses regarding the ERA questions were submitted during the post-opinion phase of the marketing authorisation procedure, showing a lack of commitment in allocating resources to ERA related issues. Therefore, the response from respondents in this study regarding the agreement to environmental risk during manufacturing being introduced within the ERA is confounding with actions of applicants noted by Caneva, et al (2014).

Despite this the overall opinion on the effectiveness of ERA in decreasing pharmaceuticals in the environment was neutral, similar to the response obtained by Doerr-MacEwen et al, (2006) when academic, industrial and government experts were questioned on the effectiveness of risk assessment regulations as management strategies. This however is in contrast to the opinion of stakeholders in this study as their opinion in terms of feasibility was skewed to being not feasible while a more positive reaction was obtained in Doerr-MacEwen et al, (2006) study.

4.1.6 Lacunae and areas of improvement

The lack of local treatment plans and an incineration plant able to handle waste generated by the facilities was noted as an improvement to the local infrastructure. It is due to this limitation in infrastructure that the local pharmaceutical manufacturing facilities need to transport waste elsewhere for incineration, thereby also increasing carbon emissions.

Through public health initiatives, many local citizens can benefit from free medications for chronic conditions such as hypertension, diabetes, asthma amongst others through the 'Pharmacy of Your Choice' scheme. The Ministry of Health through the Central Procurement and Supplies Unit has the role of tendering and purchasing medications for public and hospital use. Having a system whereby environmental impact of the medicinal

product is made a requirement is one method by which sustainable practices can be demanded from manufacturing facilities as well as applied within the post-manufacturing phase.

While some metrics are utilized by the facilities interviewed, it was noted that there is a lack of knowledge, awareness and application of green metrics. Further inclusion and awareness of what green metrics are is required at all stages of the manufacturing process, starting from research and development to the scaling-up of the process. This is an area of improvement having environmental and financial benefit as well as having a better understanding of the efficiency of processes.

This study focused on the industrial manufacturing aspect of possible methods of improvements, one needs to also take into consideration the post-manufacturing life cycle of the medication. This includes green pharmaceutical applications within hospital, community, patient use and disposal of medication. Actions should be parallelled with increased awareness and education both of patients but also of industry professionals and experts. The notion of a circular knowledge approach would allow for better management of environmental sustainability at all aspects of a medication's lifecycle.

4.2 Greenness assessment tool

When designing a synthetic pathway, factors of importance include the process economics, high yields therefore process efficiency, product quality as well as being environmentally sustainable (Gernaey et al, 2012). The scorecard developed provides a scientific and quantitative approach in the selection of green methods of synthesis.

The advantage of the tool developed is that each step of a process is evaluated and that the difference can be noted through numerical values. This is unlike the Metric Toolkit

designed by CHEM21 as described by McElroy et al (2015). In the Metric Toolkit, rather than numerical values to describe the greenness of a process, a traffic light colour system is used. Another key difference is the fact that rather than having a step-by-step approach, an overall picture starting from research and development is given. While this is beneficial to obtain an overall picture and evaluate improvements in process scale-up it does not quantify the greenness of a process as is the objective in this study.

Similarities between the developed scorecard and the Metric Toolkit include the incorporation of the solvent, catalysts, waste and notably the waste percentage metric as well as energy consumption. Differences however remain as within the developed scorecard the extended GSK solvent selection guide is used rather than the CHEM21 solvent selection guide (Alder et al, 2016). Similarly, the method of calculating energy consumption differs as within the Metric Toolkit temperature is the main consideration while time at a particular temperature, as is included within this study, is not accounted for (McElroy et al, 2015).

4.2.1 Raw materials

Raw materials are the starting point of the synthetises pathway which can have an impact on the environmental and health effects of the process (Anastas & Warner, 1998). Choices made in regard to the supply chain have an impact both on a social and environmental level (Kolotzek et al, 2018). While incorporating the life cycle of raw materials would be an ideal situation in order to distinguish between sources of the raw material and their environmental differences, due to different suppliers and complexity, a gate-to-gate approach was used in the study (Kolotzek et al, 2018). In this manner the environmental

impact of the downstream process of the product synthesis is only taken into consideration within the developed scorecard rather than both upstream and downstream.

4.2.2. Solvent selection guides and tools

As a result of the concept of green chemistry, companies such as GlaxoSmithKline have formed programs and initiatives to decrease CO_2 emissions, through the implementation of the 12 principles such as the development guides on green solvents (Taylor, 2010). Organisations such as the ASC GCI pharmaceutical roundtable were founded to promote the implementation of green initiatives in the pharmaceutical industry (Azzopardi, 2019). Various guides are now available, many similar in concept, drawing similar conclusions with the aim of classifying different solvents according to safety, health, environmental effect on air, environmental effect on water and waste (Clarke et al, 2018).[7]

The first GSK solvent sustainability guide was developed in 1992 from which various improvements and additions to the list have been made (Alder et al, 2016). The GSK guide rates solvents according to a traffic light system, namely as those having few known issues, some known issues and major known issues (Alder et al, 2016). The criteria used to evaluate this includes waste, environmental impact, impact on human health, safety and life cycle analysis (Jimenez-Gonzalez, 2004; Alder et al, 2016). The expanded GSK solvent sustainability guide which can be found within Alder et al (2016) study, was chosen to base the solvent classification score within the scorecard since each criterion is numerically scored. Different aspects of each criterion are identifiable such as for the environmental score, this comprises of the aquatic impact and air impact which each have an individual score (Alder et al, 2016).

The ACS GCI provides various tools for innovation in chemistry.[16] The solvent selection tool is designed by pharmaceutical process development experts to allow interactive selection of solvents by providing on key properties with respect to chemical functionality and physical properties.[22] The GSK solvent selection guide and CHEM21 guide differ as it simply gives details regarding the solvents rather than having an interactive aspect. Similarly to the solvent selection tool the ACS GCI also provides guides for reagents.[22] While there is a limited number of transformations that can occur, there are a variety of reagents for a particular transformation[22]. This is similar in concept to the solvent selection guides, which aid in the research and development phase to make more sustainable choices through the choice of reagents.

4.2.3 Catalysis

Catalysis is a technology on which many chemical processes both in the pharmaceutical industry as well as fine chemical industry deeply rely on (Busacca et al, 2011). Catalysts facilitate a reaction through selective enhancement or energy minimisation, having benefits of saving time, decreased waste generation and cost reduction (Busacca et al, 2011). The use of catalyst's is listed as the 9th principle of the 12 principles of green chemistry where the use of catalytic reactions which are selective as possible are a preferred reaction type to stoichiometric reactions (Anastas & Warner, 1998).

Transition metal catalysts have a vital role in industrial organic processes such as hydrogenation reactions, addition and reduction reactions (Rahman et al, 2017; Lopez and Padron, 2022). Palladium, platinum, rhodium and iridium are amongst the most widely used (Rahman et al, 2017; Lopez and Padron, 2022). While these catalysts are

[16] Tools for Innovation in Chemistry» ACS GCI Pharmaceutical Roundtable Portal [Internet]. [cited 2024 Aug 20]. Available from: https://www.acsgcipr.org/tools-for-innovation-in-chemistry/

highly efficient, issues still arise mainly regarding being a non-renewable resource, costly and due to risks of depletion of such elements (Hunt et al, 2013; Rahman et al, 2017). From this arises the necessity to find alternatives such as naturally occurring catalysts as well as methods of catalyst recovery.

Ease of catalyst recovery may be determined by whether the reaction is heterogenous and homogenous (Rahman et al, 2017). In homogenous reactions, the catalyst is in the same phase as other reactions therefore miscible resulting in separation being more difficult in comparison to heterogenous catalytic reactions (Molnár & Papp, 2017). Heterogenisation or the use of two-phase systems allow for easier separation when using homogenous complexes (Molnár & Papp, 2017). Methods of catalyst recovery include separation techniques such as solvent extraction, filtration, nano filtration, chemical precipitation, adsorption and magnetic separation (Cole-Hamilton, 2003; Rahman et al, 2017; Molnár & Papp, 2017).

4.2 Limitations

Since data obtained through the structured interview within this research study is qualitative, the best approach to validate the questionnaire would have been to conduct a pilot study to validate possible responses. This approach could not be adopted in this study since the cohort size which meets the set inclusion criteria is small and would have limited further the pool of potential participants of the study, which is already a limitation in itself.

Busy schedules and the time-consuming process of data collection were amongst reasons for participants apprehension to participate in the study in relation to the structured interviews.

When validating the developed scorecard through the application of the green and conventional synthesis pathways found in literature, certain particulars regarding the work-up processes of the experimental reactions were not listed, such as time and temperature of drying during evaporation, temperature reached for reflux and cleaning processes. It is for this reason that some of these criteria values within the scorecard could not be filled in. While various greener synthesis pathways are available for public access, the experimental details with the necessary information required in this study was a limitation. In comparison, the basic operations for Product X are more detailed however certain information is also not available therefore unable to give the most accurate interpretation and use of the tool. This is namely the amount of waste generated per step. While certain assumptions were made such as cleaning solvents being fully disposed, other reagents which were used, filtered and discarded were not able to be accounted for in the scorecard as values are not known.

4.3 Recommendations for future study

Further development to the current scorecard would aid in improvement of its intended use of quantifying the greenness of a study. Through the application of the current scorecard, one can obtain an indication of which steps are more green or less green than others, as well as compare scores between different synthesis pathways. Mathematically developing a finite range of possible values, with a maximum score indicating a greener process and minimum score indicating a less green process, is one method of improving the developed scorecard. Such a method would allow for better interpretation of the scorecard and open possibilities of setting a cutoff score to ensure the sustainability of a process.

Another method of improvement which has potential to aid the applicability and ease of use of the scorecard would be creating a database or online generator tool to calculate specific scores such as the classification score of solvents and classification score of raw materials for commonly used reagents. Development of such a tool would allow the user to easily find and input values for reagents without needing to calculate scores individually and refer to solvent selection guides or safety data sheets as these would already be compiled as a ready-to-use tool.

Possible recommendations for future studies also include conducting a focus group discussion between stakeholders within the manufacturing pharmaceutical industry to discuss lacunae and areas of improvement identified within this study. Such a focus group would also give the opportunity of an open discussion between market competitors to discuss common issues.

4.4 Conclusion

The study aids in identifying which green practices are applied locally and what the industry's perspective is on current issues pertaining to environmental impact. While increased knowledge related to pharmaceuticals in the environment has led to a drive within the pharmaceutical sector to implement sustainable practices, it can be noted that locally there is still a lack of awareness on this issue. A greater awareness on green practices is required from the industry. The major challenges identified include the financial and regulatory requirements in implementing changes. The introduction of a legal framework and regulatory support on the introduction of green practices would contribute to change in current practices.

The scorecard developed allows for the quantification of the greenness of a process allowing for comparisons of different procedures thereby contributing to the use of

greener methods of API synthesis. The scorecard is a holistic approach of assessing a synthesis process. In this study, it was demonstrated how the scorecard developed can quantitively distinguish between a green and less green conventional synthesis pathway as well as how different processing parameters may affect the sustainability of a process such as temperature.

The issue of safeguarding the environment has been a growing concern internationally in all parts of society. This study aids this cause as it highlights current applications of green pharmaceutical practices and areas of improvement within the industry. It also provides a practical tool thus facilitating sustainable efforts from a manufacturing perspective.

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Appendix 1

Questions for Interview

Industry type: _____

Position: _____

1. About the company
    a. How many employees form part of the company?
    b. What type of product is produced by the company?
    c. How many products are produced per year within the facility?
    d. Is your annual turnover:

        ☐ less than 2 million
        ☐ between 2 and 10 million
        ☐ between 10 and 50million
        ☐ greater than 50 million?

    e. Is your balance sheet value:

        ☐ less than 2 million
        ☐ between 2 and 10 million
        ☐ between 10 and 43 million
        ☐ greater than 43 million?

2. Pharmaceutics in the environment
    a. Are you concerned about pharmaceutical concentrations within the environment? Why?
    b. Do you think that Malta and the EU is at the stage of management action or risk assessment in regards to pharmaceutical's within the environment?

3. Knowledge and opinion regarding green pharmaceutical practices
    a. Have you ever heard of green pharmaceutical practices?

(If YES) i. From where have you heard of green pharmaceutical practices?

b. Do you apply green practices within the manufacturing?

(IF YES) i. What are the positive remarks about implementing green practices?

c. What are the barriers and challenges to implementing green practices?

d. Do you think that there is enough information available regarding green pharmaceutical practices?

4. Green Pharmaceutical practices implemented

a. What green pharmaceutical practices are implemented?

☐ Green Metrics

☐ Wastewater treatment systems
☐Renewable energy
☐ Green solvents
☐ Solvent Recovery
☐ Continuous manufacturing
☐ One pot synthesis
☐Paperless Approach
☐ Other -

_____

Green Metrics

(IF USED)

i. Which green metrics are used?

(IF NOT USED)

ii. Why are green metrics not applied within the manufacturing process?

iii. Do you think in the future these will be applied?

Wastewater treatment systems

i. Are conventional or advanced methods used? Can you mention these?

ii. Is wastewater prevention or wastewater treatment the preferred method of decreasing wastewater. Why?

Renewable energy

(IF USED)

i. What percentage of energy consumption is from renewable sources

ii. What are the renewable energy sources used?

iii. What have been the benefits observed since implementation?

(IF NOT USED)

iv. What are the reasons against its implementation?

v. Why are renewable energy sources not used?

vi. Do you think use of renewable energy is in the pipeline for the future?

Green solvents

(BOTH)

i. When selecting solvents do you consider the environmental impact?

(IF USED)

ii. Why have you opted to use green solvents over other solvents

(IF NOT USED)

iii. Why are green solvents not used?

iv. In what situations do you think green solvents could be used?

Solvent Recovery

(IF USED)

i. Is solvent recovery a common practice such that it is involved in majority of processes within the facility? Can you indicate the percentage of solvents recovered?

ii. What are those solvents most commonly recovered?

(IF NOT USED)

iii. Why is solvent recovery not used?

iv. Would you consider solvent recovery in the future?

Paperless Approach

(IF USED)

i. What have been the benefits observed so far?

(IF NOT USED)

ii. Do you think you will implement this in the future?

5. Reduction of waste

a. Do you have any suggestions on how to reduce pharmaceutical waste within the industry (e.g. during production)?

b. Currently the EU within the pharmaceutical strategy are discussing reduction of packaging size to reduce waste. What are your thoughts about this? How do you think this will affect the manufacturing industry? Do you have any suggestions on how to reduce pharmaceutical waste within the industry (e.g. during production)?

6. Revision of GMPS
    a. Currently GMPs published by EMA do not cover the control of emissions of pharmaceutical products and residues. Do you think this should be extended such that GMPs would outline standards for discharge of pharmaceutical residues?
    b. What would the implication of such GMPs be on the company?

7. Procurement of raw materials and APIs?
    a. China and India are amongst the biggest manufacturers of APIs and raw materials. Do you think that the EU should impose quality marks for pollution control on these materials manufactured since these products are a major import for the EU?

8. Environmental Risk Assessment and Benefit to risk assessment
    a. As by Directive 2001/83/EC Article 8 (3), assessment of the undesired effects on the environment and potential risks on exposure of the medicinal product is required during the application for a marketing authorisation. Should an inclusion regarding environmental risks and burden of the drug during manufacturing rather than only on the use of the product be included in the environmental risk assessment?
    b. Should the environmental risk assessment constitute as a criterion for refusal if the impact on the environment is considered substantial?
    c. Should the environmental risks of a medicinal product be part of the products pharmacovigilance?

d. From a score of 1-5 with:

1 = not at all, 2 = slightly, 3 = moderately, 4 = very, 5 = extremely

	1	2	3	4	5
i. How effective do you think that environmental risk assessment regulations would be in decreasing pharmaceuticals in the environment?					
Why?					
ii. Do you think that environmental risk assessment regulations are feasible in decreasing pharmaceuticals in the environment?					
Why?					

9. Willingness to pay of the company

a. Would you be willing to pay a fee to aid in research regarding green initiatives and provide educational campaigns. What other situations would you be willing to pay in order to make the manufacturing industry more sustainable?

(IF YES)

i. How much would you be willing to pay? What percentage of yearly profits would this be?

(IF NO)

ii. What are the reasons behind this?

b. What are your thoughts on the implications of including such a fee on medicines such that this increase will fund green initiatives and make information regarding the environmental impact more available?

10. Incentives

a. What incentivises you to adopt green practices?

b. Do you think that if incentives for company's striving to be greener (e.g. development of green drugs, investment in new WWTP) were in place locally such as a monetary prize, more innovations would be developed to meet green ideals?

c. Are you in agreement of imposing fines on pharmaceutical companies that do not implement green practices within manufacturing?

d. Are you in agreement of imposing fines on pharmaceutical companies that do not ensure safe emission levels of pharmaceuticals into the environment?

e. From a score of 1-5 with:

1 = not at all, 2 = slightly, 3 = moderately, 4 = very, 5 = extremely

	1	2	3	**4**	5
i. How effective do you think incentives for the development of green drugs be in decreasing pharmaceuticals in the environment?					
Why?					
ii. How feasible is it to have these incentives in the development of green drugs?					
Why?					

Appendix: 2

Ethics Approval

L-Università ta' Malta

Christine Gauci <christine.gauci.19@um.edu.mt>

The status of your REDP form (MED-2023-00491) has been updated to Acknowledged

1 message

form.urec@um.edu.mt <form.urec@um.edu.mt> 5 January 2024 at 11:15
To: christine.gauci.19@um.edu.mt

Dear Christine Gauci,

Please note that the status of your REDP form (MED-2023-00491) has been set to *Acknowledged*.

This status change was accompanied by the following explanation/justification: *Dear applicant, Your research ethics application has been received. This does not mean that your application has FREC ethical approval and may be subject to an audit review. The FREC number generated by submission for records only cannot be used as proof of ethical approval. As indicated in the Research Ethics Review Procedures, submissions which have no self-assessment issues are kept for record and audit purposes only, so research may commence. Kindly note that FREC will not issue any form of approval as the responsibility for the self-assessment part lies exclusively with the researcher. Please note that SCPD generally requires review. If you have any questions or doubts or require any further clarification you can contact the MED FREC secretary. Regards, MED FREC*

You can keep track of your applications by visiting: https://www.um.edu.mt/research/ethics/redp-form/frontEnd/.

This email has been automatically generated by URECA. Please do not reply. If you wish to communicate with your F/REC please use the respective email address.

Appendix: 3

Abstract for poster submission for the FIP World Congress of Pharmacy and Pharmaceutical Sciences

Green Pharmaceutical Practices in Industry: A review

Christine Gauci, Nicolette Sammut Bartolo, Anthony Serracino-Inglott

Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta

Background: The increased use of pharmaceutical products and greater awareness of the environment has resulted in increased subtherapeutic concentrations of active pharmaceutical ingredients being detected in the environment. Each stage of a pharmaceutical products lifecycle contributes to the issue of pharmaceutical pollution with the manufacturing industry being the focus of this study. The application of green pharmaceutical practices during pharmaceutical processes strive to minimise the environmental impact of the pharmaceutical industry.

Purpose: To identify green pharmaceutical practices applied in manufacturing industry which reduce environmental impact.

Method: A literature review was conducted to identify and evaluate the green practices implemented in the manufacturing industry. This was carried out by searching for related terms such as “green pharmaceutical practices”, “green chemistry” and “green pharmacy” using the databases Google Scholar, PubMed and Hydi which is a collection of databases available at the University of Malta. Articles were analysed according to relevancy to the topic in question.

Results: The green pharmaceutical practices utilised within the manufacturing industry identified through the literature review mainly related to 4 broad categories: solvents and their use, wastewater treatment systems, renewable energy and green chemistry.

Solvent recovery and solventless synthesis where measures identified in reducing solvent use in manufacturing processes. Use of green solvents and solvent selection guides were identified as safer and more efficient alternatives in developing sustainable choices especially at the research and development phase. Wastewater treatment systems are a necessity to reduce organic and slow biodegrading contaminants. These can be subdivided into conventional treatment processes, such as conventional activated sludge processes which are the more commonly applied due to low cost and effectiveness, and advanced treatment processes. Advanced treatment processes are more efficacious processes in removing pollutants from water used in secondary wastewater treatment with techniques identified including advanced oxidation and membrane filtration processes. In terms of renewable energy, solar energy, as an alternative for heat and energy generation, and fuel cells, as an alternative to combustion engines and boilers, were identified as providing cleaner energy and reduced emissions. Use of green metrics such as atom economy, process mass intensity, process yield and E-factor aid in optimisation by quantifying efficiency and environmental impact. Continuous manufacturing was identified as an alternative to batch manufacturing, noted to reduce material and energy use, while a one pot synthesis approach reduced solvent and waste production by removing isolation and purification steps.

Conclusion: Different measures along the pharmaceutical lifecycle are necessary to decrease the environmental impact of the pharmaceutical industry. As the environmental consequences are being made more evident through continuous studies, reports and field testing, enforcement of new legislations is key in ensuring a more sustainable future

Appendix: 4

Poster presentation for the FIP World Congress of Pharmacy and Pharmaceutical Sciences

L-Università ta' Malta Faculty of Medicine & Surgery | Department of Pharmacy

Green Pharmaceutical Practices in Industry: A Review

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INTRODUCTION

Increased use of pharmaceuticals and awareness of the environment has led to the detection of subtherapeutic concentrations of drugs in the environment.[1] Green pharmaceutical practices when applied in pharmaceutical processes, minimise the environmental impact of the activities related to the pharmaceutical industry.[2]

AIMS

To identify green pharmaceutical practices applied in the pharmaceutical manufacturing industry.

METHOD

A literature review was conducted to identify and evaluate green practices implemented in the manufacturing industry. This was carried out by searching for terms such as "green pharmaceutical practices", "green chemistry" and "green pharmacy" in Google Scholar, PubMed and Hydi; a collection of databases available at the University of Malta. Articles were analysed according to relevance to the topic in question.

RESULTS

- The 12 principles of green chemistry developed by Anasatas and Warner in 1998 were identified as the bases for green pharmaceutical practices.[3]
- Practices applied within the pharmaceutical industry are related to four groups (Fig 1).
- Solvent recovery and solventless synthesis reduce the use of solvents and related waste generated.
- Green solvents are alternatives to traditional organic solvents providing sustainable options.
- Wastewater treatment systems reduce organic and slow biodegrading contaminants.
- Solar energy and fuel cells provide alternatives to combustion engines and boilers.
- Ensuring facility maintenance such as upkeep of insulation and fittings ensures energy efficiency.
- Green metrics such as atom economy and E-factor allow for the quantification of efficiency and environmental impact of processes.

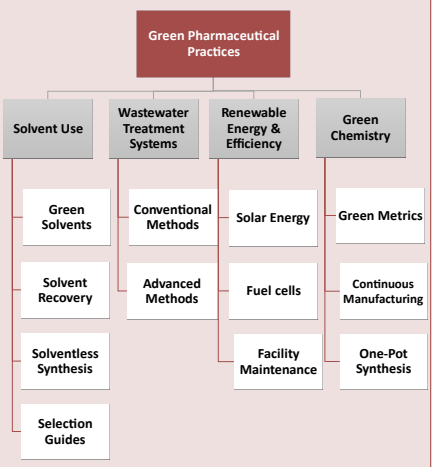

Figure 1 : Green Pharmaceutical Practices Identified Through Literature Review

CONCLUSION

Different measures along the pharmaceutical product lifecycle are necessary to decrease environmental impact. As the environmental consequences are being made more evident through continuous studies, reports and field testing, enforcement of new legislations is key in ensuring a more sustainable future.

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Appendix: 5

Greenness assessment tool application of conventional method of piperazine-azole-fluoroquinolone based 1,2,4-triazole derivative synthesis (Basoglu Ozdemir et al, 2018)

Step Number			1	2	3	4	5	6a	6b	6c	6d	7a	7b
Raw Material Score		∑of individual RMS	29	9	13	7	16	17	17	17	17	11	17
Catalyst Score		Depletion	0	0	0	0	0	0	0	0	0	0	0
		Recoverability	0	0	0	0	0	0	0	0	0	N/A	N/A
		Efficiency	0	0	0	0	0	0	0	0	0	1.33	1.31
Solvent score		Classification	42	112.5	121.5	42.5	37	80	80	69	69	40	40
		Solvent used per product	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Energy Consumption Score		time point x temperature point	1	8	1	6	4	3	3	3	3	8	8
Cleaning		No. of steps	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		classification	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Cleaning score	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Waste Generated	**Aqueous**	Type	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		% waste	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Waste recovered	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Organic	Type	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		% waste	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Waste recovered	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Yield %			75	91	50	65	83	65	73	25	54	75	76
Atom Economy			N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total Per Step			72	129.5	135.5	55.5	57	100	100	89	89	60.33	66.31

Step Number	**8a**	**8b**	**9a**	**9c**	**10**	**11a**	**11b**	**12a**	**12b**	**13**	**14**	**15a**	**15b**
∑of individual RMS	13	13	24	24	14	17	17	11	17	9	5	17	17
Depletion	0	0	0	0	0	0	0	0	0	0	0	0	0
Recoverability	N/A	N/A	0	0	0	0	0	N/A	N/A	0	0	0	0
Efficiency	5	5	0	0	0	0	0	1.42	2	0	0	0	0
Classification	74	74	102	103	110	80	80	40	40	45.5	34	80	80
Solvent used per product	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
time point x temperature point	6	6	3	3	4	3	3	8	8	6	2	3	3
No. of steps	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
classification	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cleaning score	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Type	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
% waste	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Waste recovered	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Type	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
% waste	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Waste recovered	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Yield %	60	60	24	15	53	25	78	70	50	54	75	45	32
Atom Economy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total per step	98	98	129	130	128	100	100	60.42	67	60.5	41	100	100
Total per process	2166.1												

Appendix 6:

Greenness assessment tool application of green method of piperazine-azole-fluoroquinolone based 1,2,4-triazole derivative synthesis (Basoglu Ozdemir et al, 2018)

Step Number			**1**	**2**	**3**	**4**	**5**	**6a**	**6b**	**6c**	**6d**	**7a**	**7b**
Raw Material Score		∑of individual RMS	28	9	12	7	16	26	26	26	26	9	9
Catalyst Score		Depletion	0	0	0	0	0	0	0	0	0	0	0
		Recoverability	0	0	0	0	0	0	0	0	0	N/A	N/A
		Efficiency	0	0	0	0	0	0	0	0	0	1.12	1.19
Solvent score		Classification	76	78.5	121.5	42.5	42.5	80	80	80	80	40	40
		Solvent used per product	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Energy Consumption Score		time point x temperature point	3	2	2	3	2	2	3	2	3	2	2
Cleaning		No. of steps	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Classification	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Cleaning score	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Waste Generated	**Aqueous**	Type	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		% waste	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Waste recovered	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Organic	Type	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		% waste	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Waste recovered	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Yield %			90	96	87	77	90	80	84	49	70	89	84
Atom Economy			N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total per step			107	89.5	135.5	52.5	60.5	108	109	108	109	52.12	52.19

Step Number	**8a**	**8b**	**9a**	**9c**	**10**	**11a**	**11b**	**12a**	**12b**	**13**	**14**	**15a**	**15b**
∑of individual RMS	13	13	24	24	8	26	26	3	3	9	5	26	26
Depletion	0	0	0	0	0	0	0	0	0	0	0	0	0
Recoverability	N/A	N/A	0	0	0	0	0	N/A	N/A	0	0	0	0
Efficiency	4.17	4	0	0	0	0	0	1.14	1.42	0	0	0	0
Classification	74	74	102	102	110	80	80	40	40	28.5	34	80	80
Solvent used per product	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
time point x temperature point	2	2	3	3	2	2	2	2	2	2	2	2	2
No. of steps	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Classification	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cleaning score	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Type	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
% waste	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Waste recovered	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Type	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
% waste	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Waste recovered	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Yield %	72	75	45	50	78	55	85	87	70	77	94	58	55
Atom Economy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total per step	93.17	93	129	129	120	108	108	46.14	46.42	39.5	41	108	108
Total per process	2152.5												

Appendix: 7

Greenness assessment tool application of conventional method of N-substituted pyrrole derivatives synthesis (Clauson-Kaas & Tyle, 1952)

Step Number			**1**	**2**	**3**	**4**
Raw Material Score		∑of individual RMS	24	16	0	20
Catalyst Score		Depletion	0	0	1	0
		Recoverability	0	0	2	0
		Efficiency	0	0	0.62	0
Solvent score		Classification	50	86	36	89
		Solvent used per product	1	1	1	1
Energy Consumption Score		time point x temperature point	2	2	1	2
Cleaning		No. of steps	N/A	N/A	N/A	N/A
		classification	N/A	N/A	N/A	N/A
		Cleaning score	N/A	N/A	N/A	N/A
Waste Generated	**Aqueous**	Type	N/A	N/A	N/A	N/A
		% waste	N/A	N/A	N/A	N/A
		Waste recovered	N/A	N/A	N/A	N/A
	Organic	Type	N/A	N/A	N/A	N/A
		% waste	N/A	N/A	N/A	N/A
		Waste recovered	N/A	N/A	N/A	N/A
Yield %			95	96	97	88
Atom Economy			N/A	N/A	N/A	N/A
Total per step			77	105	41.62	112
Total per process			335.62			

Appendix: 8

Greenness assessment tool application of green method of N-substituted pyrrole derivatives synthesis (Khammas et al, 2018)

Step Number			**1**	**2**
Raw Material Score		∑of individual RMS	6	23
Catalyst Score		Depletion	0	0
		Recoverability	0	0
		efficiency	0	0.45
Solvent score		Classification	50	78.5
		Solvent used per product	4	N/A
Energy Consumption Score		time point x temperature point	2	0
Cleaning		No. of steps	N/A	N/A
		Classification	N/A	N/A
		Cleaning score	N/A	N/A
Waste Generated	**Aqueous**	Type	N/A	N/A
		% waste	N/A	N/A
		Waste recovered	N/A	N/A
	Organic	Type	N/A	N/A
		% waste	N/A	N/A
		Waste recovered	N/A	N/A
Yield %			N/A	88
Atom Economy			N/A	N/A
Total per step			62	101.95
Total per process			163.95	

Appendix: 9

Assessment tool application for synthesis of Product X as a pilot study

Synthesis Pathway A			Purge	Charge	Cool	Charge	Heat + stir	Charge + stir	Charge + stir	Decant	Charge	Heat/cool + distil	Filter + Clean
Step Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Raw Material Score		∑of individual RMS	2			17					6		
Catalyst Score		Depletion											
		Recoverability											
		Efficiency											
Solvent score		Classification		45				45	20.5				
		Solvent used per product		1				1	1				
Energy Consumption Score		time point x temperature point			2	2	1	3	1			8	
Cleaning		No. of steps											2
		Classification											27.5
		Cleaning score											55
Waste Generated	**Aqueous**	Type								N/A			
		% Waste								N/A			
		Waste recovered								2			
	Organic	Type											3
		% Waste											12.52
		Waste recovered											2
Yield %													
Atom Economy													
Total per step			2	46	2	19	1	49	22.5	2	6	8	72.52
Total per process			230.02										

Synthesis Pathway B - Part 1			purge	charge + cool	charge	heat & stir	charge + cool	charge	heat & stir	charge	heat & cool	cool +stir	filter &wash
Step Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Raw Material Score		∑of individual RMS	2		9		7	6					
Catalyst Score		Depletion											
		Recoverability											
		Efficiency											
Solvent score		Classification		27.5			27.5			18.5			
		Solvent used per product		1			1			1			
Energy Consumption Score		time point x temperature point		2	2	3	2	2	1		2	1	0
Cleaning		No. of steps											1
		Classification											50
		Cleaning score											50
Waste Generated	**Aqueous**	Type											0
		% Waste											24.7
		Waste recovered											2
	Organic	Type											4
		% Waste											45.28
		Waste recovered											2
Yield %													
Atom Economy													
Total Per Step			2	30.5	11	3	37.5	8	1	19.5	2	1	127.98

Synthesis Pathway B - Part 2			Purge	Charge	Heat + stir	Cool + stir	Filter +clean
Step Number			**1**	**2**	**3**	**4**	**5**
Raw Material Score		∑of individual RMS	2				
Catalyst Score		Depletion					
		Recoverability					
		Efficiency					
Solvent score		Classification		50			
		Solvent used per product		2			
Energy Consumption Score		time point x temperature point			2	1	
Cleaning		No. of steps					1
		Classification					50
		Cleaning score					50
Waste Generated	**Aqueous**	Type					0
		% Waste					23.38
		Waste recovered					2
	Organic	Type					4
		% Waste					29.72
		Waste recovered					2
Yield %							
Atom Economy							
Total per step			2	52	2	1	111.1
Total per process			411.58				

Synthesis Pathway C – Part 1			Purge	charge	Charge + heat	Charge + cool	Charge + cool	Filter + Clean	Clean	Purge	Charge + stir	Charge + stir	Cool + Stir	Filter + Clean
Step Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Raw Material Score		∑of individual RMS	2		4	13				2				
Catalyst Score		Depletion												
		Recoverability												
		Efficiency												
Solvent score		Classification		31.5	18		18				33	33		
		Solvent used per product		1	1		1				1	1		
Energy Consumption Score		time point x temperature point		1	1	1	2				1	1	2	
Cleaning		No. of steps						3	1					2
		Classification						18	33					33
		Cleaning score						54	33					66
Waste Generated	**Aqueous**	Type						0						
		% Waste						9.41						
		Waste recovered						2						
	Organic	Type							4					4
		% Waste							21.04					9.39
		Waste recovered							2					2
Yield %														
Atom Economy														
Total Per Step			2	33. 5	24	14	21	65.41	60.04	2	35	35	2	81.39

Synthesis Pathway C – Part 2			Purge	Charge + stir	Cool + stir	Filter + Clean	Dry
Step Number			**13**	**14**	**15**	**16**	**17**
Raw Material Score		∑of individual RMS	2				
Catalyst Score		Depletion					
		Recoverability					
		Efficiency					
Solvent score		Classification		20.5			
		Solvent used per product		1			
Energy Consumption Score		time point x temperature point		1	2		2
Cleaning		No. of steps				3	
		Classification				20.5	
		Cleaning score				61.5	
Waste Generated	**Aqueous**	Type					
		% Waste					
		Waste recovered					
	Organic	Type				4	
		% Waste				10.75	
		Waste recovered				2	
Yield %							
Atom Economy							
Total per step			2	22.5	2	78.25	76.25
Total per process			556.34				

Synthesis Pathway D			Purge	Charge + Stir	Filter + Clean	Charge + stir	Filter + Clean	Clean	Dry
Step Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**
Raw Material Score		∑of individual RMS	2			9			
Catalyst Score		Depletion							
		Recoverability							
		Efficiency							
Solvent score		Classification		45		45			
		Solvent used per product		1		1			
Energy Consumption Score		time point x temperature point		1	1	1			2
Cleaning		No. of steps			1		1	2	
		Classification			45		45	20.5	
		Cleaning score			45		45	41	
Waste Generated	**Aqueous**	Type							
		% Waste							
		Waste recovered							
	Organic	Type			7		7	4	
		% Waste			10.28		10.28	10.28	
		Waste recovered			2		2	2	
Yield %									
Atom Economy									
Total per step			2	47	65.28	56	64.28	57.28	2
Total per process			293.84						

Addendum

Step Number		1	2	3	4	5	6	7
Raw Material Score	∑of individual RMS							
Catalyst Score	Depletion							
	Recoverability							
	Efficiency							
Solvent score	Classification							
	Solvent used per product							
Energy Consumption Score	time point x temperature point							
Cleaning	No. of steps							
	Classification							
	Cleaning score							
Waste Generated	Aqueous Type							
	Aqueous % Waste							
	Aqueous Waste recovered							
	Organic Type							
	Organic % Waste							
	Organic Waste recovered							
Yield %								
Atom Economy								
Total Per Step								

Raw Material Score (RMS)

Based on the GHS hazard classification system. Information related to GHS classification can be obtained from safety data sheets and the database PubChem.
Each hazard statement code is denoted with the letter H. The first number of the hazard statement indicates the type of hazard namely: 2 refers to Physical hazards, 3 indicates Health hazards and 4 refers to Environmental hazards.

Using GHS: The individual raw material score is calculated according to the number of GHS hazard statements and whether the hazard statement includes

RMS = [(∑Physical + ∑Health + ∑Environmental statements) x 1 (Warning)] + [(∑Physical + ∑Health + ∑Environmental statements) x 2 (Danger)]

Raw Material Name	Warning			Danger			RMS
	∑Physical	∑Health	∑Environmental	∑Physical	∑Health	∑Environmental	

Solvent Score

Using Values from the GSK Solvent selection guide

Solvent Classification Score = 100-[(Waste) x0.5 + (Environmental Impact + Health) x1.5 + flammability + reactivity]

Solvent Name							
Waste							
Environmental							
Health							
Flammability							
Reactivity							
Waste CS							
Environmental CS							
Health CS							
Solvent CS	100	100	100	100	100	100	

To calculate the solvent used per mass product product :

$$\textit{Mass Intensity} = \frac{\textit{Solvent used}}{\textit{Total Mass Produced}}$$

Mass Intensity	Penalty Point
>10 L/kg product	1
10-15 L/kg product	2
15-20 L/kg product	3

Solvent score = Solvent classification score x Mass Intensity Penalty Point

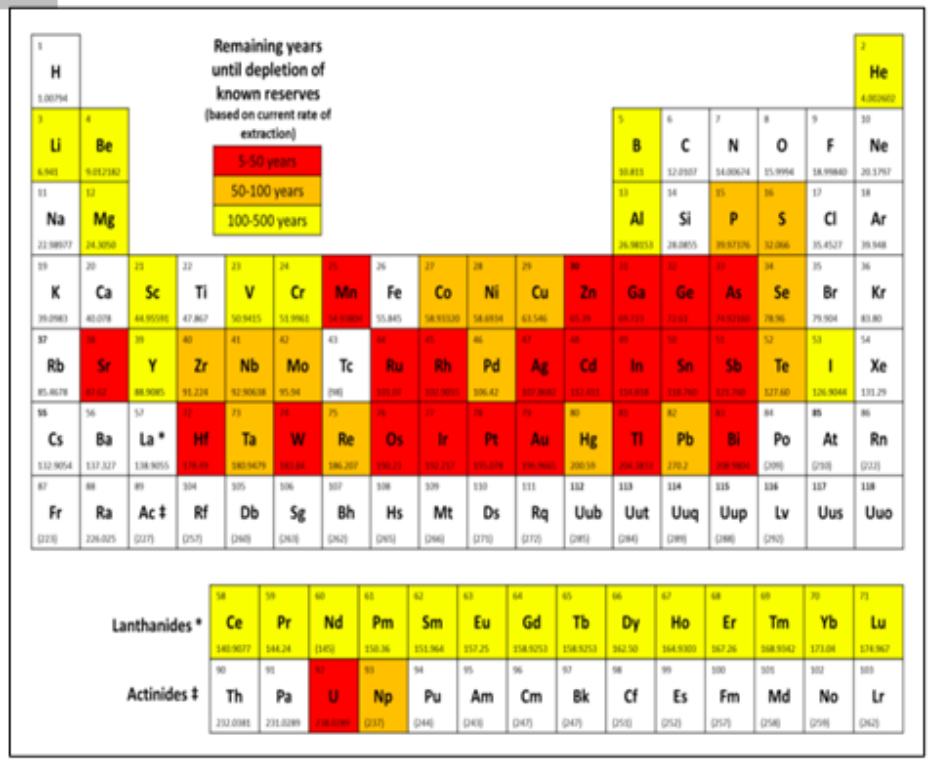
Catalyst Score	
Depletion risk	
5-50 years	2
50-100years	1
100-500years	0
not known	0

Recoverabillity	
Yes, Rcovered	0
No, Not Recovered	2

$$Turnover\ Number = \frac{Moles\ of\ Limiting\ Reactant}{Moles\ of\ Catalyst} \times Yield$$

$$Efficiency = \frac{1}{Turnver\ Number}$$

$$Catalyst\ score = Depletion\ risk + recovery\ penalty\ point + \frac{1}{Turnover\ number}$$



Cleaning score

Using Values from the GSK Solvent selection guide

Solvent Classification Score = 100-[(Waste) x0.5 + (Environmental Impact + Health) x1.5 + flammability + reactivity]

Solvent Name										
Waste										
Environmental										
Health										
Flammability										
Reactivity										
Waste CS										
Environmental CS										
Health CS										
Solvent CS	100	100	100	100	100	100	100	100	100	100

Cleaning Score per Solvent used = Solvent Classification Score x No. of steps involving solvent

Energy Consumption

Temperature range	Penalty Point
20°C to 70 °C	1
0°C - 20°C 70°C - 140 °C	2
< 0°C & > 40 °C	3

Time of reaction	Penalty Point
≥5 hours	1
5 - 10 hours	2
10 - 24 hours	3
≤ 24hours	4

Energy Consumtpion Score = temperature range penalty point X Time of Reaction penalty point

Waste Generated

Waste type = [(∑Physical + ∑Health + ∑Environmental statements) x 1 (Warning)] + [(∑Physical + ∑Health + ∑Environmental statements) x 2

Waste Intensity (WI) = Total waste produced / Total mass input

Process Mass Intensity (PMI) = Total mass in step / Product mass

Waste % = Waste Intensity / Process Mass Intensity X 100

Total waste produced									
Total mass input									
Waste intensity									
Total mass in step									
Product mass									
Process mass intensity									
Waste %									

Other Metrics

$$\text{Yield \%} = \frac{\text{Moles of product}}{\text{Moles of limiting reactant}} \times 100$$

Moles of product						
Moles of limiting reactant						
yield %						

$$\text{Atom Economy} = \frac{\text{Molecular weight of product}}{\text{Total molecular weight of reactants}} \times 100$$

MV of product						
Total molecular weight of ractants						
Atom Economy						